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"Prediabetes" diagnosis less useful in older patients

Large study supports a focus on healthy lifestyle changes as findings show that older adults deemed "prediabetic" seldom progress to full diabetes

Older adults who are classified as having "prediabetes" due to moderately elevated measures of blood sugar usually don't go on to develop full-blown diabetes, according to a study led by researchers at Johns Hopkins Bloomberg School of Public Health.

Doctors still consider prediabetes a useful indicator of future diabetes risk in young and middle-aged adults. However, the study, which followed nearly 3,500 older adults, of median age 76, for about six and a half years, suggests that prediabetes is not a useful marker of diabetes risk in people of more advanced age.

The results were published February 8 in *JAMA Internal Medicine*.

"Our results suggest that for older adults with blood sugar levels in the prediabetes range, few will actually develop diabetes," says study senior author Elizabeth Selvin, PhD, professor in the Department of Epidemiology at the Bloomberg School. "The category of prediabetes doesn't seem to be helping us identify high-risk people. Doctors instead should focus on healthy lifestyle changes and important disease risk factors such as smoking, high blood pressure, and high cholesterol."

Type 2 diabetes leads to a chronically excess blood level of glucose, which stresses organs including the kidneys, weakens the immune system, and damages blood vessels, promoting heart disease and stroke among other conditions. The prevalence of diagnosed type 2 diabetes in the United States has gone from less than one percent in the 1950s to more than 7 percent today--and researchers believe that the actual figure now, including undiagnosed diabetes, is over 12 percent. This sharp increase is due to the aging U.S. population and increased rates of overweight and obesity.

Doctors have used the concept of prediabetes--involving blood glucose levels that are higher than normal but not yet in the diabetic range--as an indicator of elevated diabetes risk in younger and middle-aged people. However, the utility of the concept in older adults--especially those 70 and older--has been less clear.

"It's very common for older adults to have at least mildly elevated blood glucose levels, but how likely they are to progress to diabetes has been an unresolved question," Selvin says.

To get a better picture of how older adults with prediabetes fare, Selvin and colleagues turned to the Atherosclerosis Risk in Communities Study. This large epidemiological cohort project, funded by the U.S. National Heart, Lung, and Blood Institute and including both Black and white participants, has been running at four U.S. medical centers, including Johns Hopkins, since 1987. For their prediabetes analysis, the researchers selected 3,412 ARIC study participants who had attended a follow-up visit during 2011-13--a time when the participants were between 71 and 90 years old--and did not have any history of diabetes. The researchers then looked at how measures of the participants' blood glucose levels had changed at the next follow-up visit during 2016-17.

As expected, the researchers found that "prediabetes," defined according to two different blood-test measures, was very common among the participants at the 2011-13 visit. Those with prediabetes, defined by moderately high blood levels of glucose following overnight fasting (the impaired fasting glucose test, or IFG), represented 59 percent of the initial sample, and those with prediabetes defined with a different blood test for glycated hemoglobin (HbA1c), represented 44 percent of the initial sample.

However, the results showed that only small numbers of the participants who had prediabetes in 2011-13 had developed diabetes by the time of the 2016-17 visit--8 percent of the IFG-defined prediabetics, and 9 percent of the HbA1c-defined

prediabetics.

By contrast, 44 percent of the IFG group and 13 percent of the HbA1c group had improved enough by the 2016-17 visit that their test results were back in the normal range. Moreover, 16 and 19 percent of these two groups had died of other causes by the 2016-17 visit.

The results show that older adults with prediabetes, over intervals like the one in the study, are more likely to have lower blood sugar levels--or to die for other reasons--than to progress to diabetes.

"It appears that in older adults, 'prediabetes' is just not a robust diagnosis," Selvin says.

"Our findings support a focus on lifestyle improvements, including exercise and diet when feasible and safe, for older adults with prediabetes," says Mary Rooney, PhD, a postdoctoral fellow at the Bloomberg School and the paper's first author. "This approach has broad benefits for patients."

Selvin and her colleagues recommend that for older adults, physicians should focus their screening efforts on risk factors, such as hypertension, that are more useful in predicting illness and mortality in this population.

"Risk of Progression to Diabetes Among Older Adults with Prediabetes" was authored by Mary Rooney, Andreea Rawlings, James Pankow, Justin Echouffo Tcheugui, Josef Coresh, Richey Sharrett, and Elizabeth Selvin.

Funding was provided by the NHLBI (T32HL007024, K24HL152440) and by the National Institute of Diabetes and Digestive and Kidney Diseases (R01DK089174).

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Ancient owl vomit helps researchers unpack prehistoric bone secrets

Researchers studying one of the oldest collections of ancient animal bones in the world have used DNA still present in the bones to identify 17 animal species

Curtin University researchers studying one of the oldest collections of ancient animal bones in the world have used DNA still present in the bones to identify 17 animal species, including two rodents previously not known to be in the collection.

Lead researcher Dr. Frederik Seersholm, Ph.D. candidate from Curtin's Trace and Environmental DNA (TrEnD) Laboratory at the School of Molecular and Life Sciences, said the research involved ancient bones collected during cave excavations done in Brazil in the 1800s by Danish naturalist P.W. Lund, who was famous for his description of giant prehistoric animals such as the South American saber-toothed cat and giant sloths.

"Lund decided to donate his entire fossil collection to the King of Denmark and in 1845 hundreds of wooden boxes of the bones were carried by mule from Lagoa Santa to the port of Rio de Janeiro, Brazil and shipped to Copenhagen," Dr. Seersholm said.

"Unfortunately for the collection, the king died in 1848 shortly after it arrived and the vast majority of the more than 100,000 ancient bone fragments were never formally described—until now."

Dr. Seersholm said the analysis, done in collaboration with the University of Copenhagen, demonstrated the potential for ancient DNA studies on P.W. Lund's famous bone collection.

"In this study we show that even though the collection is old, and has had a very 'rough' life with long periods of terrible storage locations, DNA is still present in the bones," Dr. Seersholm said.

"This finding has tremendous implications for future studies of the collection, which holds thousands of ancient bones still to be analysed.

"By analysing 100 small bone fragments from P.W. Lund's collection with carefully optimised ancient DNA methods, we were able to genetically identify 17 species, representing 11 mammals, two birds, one fish, and three frogs—and of these, two species of rodent that have never before been described in the collection."

The researchers analysed samples of owl regurgitation excavated from caves by P.W. Lund in the 1840s and sequenced short DNA

fragments to identify different species. The study was undertaken by an international team led by Professor Morten Allentoft, also from Curtin's TrEnD Lab at the School of Molecular and Life Sciences.

Professor Allentoft said the findings could suggest that the negative effects of poor storage conditions are negligible compared with the long-term DNA degradation that bone specimens undergo in the environment before excavation.

"So far, successful genetic research on the material collected by Lund has been limited to two samples of human skull bone, but with the identification of well-preserved DNA in even the smallest of bones from the collection, we now know that its potential for exciting ancient DNA research is much greater than anyone anticipated," Professor Allentoft said.

"There is without doubt a great deal of information to be retrieved from the fragmented bones of P.W. Lund's collection, and it is likely that the collection holds important future discoveries of extinct South American species." The study, "Ancient DNA preserved in small bone fragments from the P.W. Lund collection," was published in journal *Ecology and Evolution*.

More information: *Frederik V. Seersholm et al. Ancient DNA preserved in small bone fragments from the P.W. Lund collection, Ecology and Evolution (2021). DOI: 10.1002/ece3.7162*

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MSK researchers learn what's driving 'brain fog' in people with COVID-19

Presence of inflammatory molecules in the cerebrospinal fluid

One of the dozens of unusual symptoms that have emerged in COVID-19 patients is a condition that's informally called "COVID brain" or "brain fog." It's characterized by confusion, headaches, and loss of short-term memory. In severe cases, it can lead to psychosis and even seizures. It usually emerges weeks after someone first becomes sick with COVID-19.

In the February 8, 2021, issue of the journal *Cancer Cell*, a multidisciplinary team from Memorial Sloan Kettering reports an underlying cause of COVID brain: the presence of inflammatory molecules in the liquid surrounding the brain and spinal cord (called the cerebrospinal fluid). The findings suggest that anti-inflammatory drugs, such as steroids, may be useful for treating the condition, but more research is needed.

"We were initially approached by our colleagues in critical care medicine who had observed severe delirium in many patients who were hospitalized with COVID-19," says Jessica Wilcox, the Chief Fellow in neuro-oncology at MSK and one of the first authors of the new study. "That meeting turned into a tremendous collaboration between neurology, critical care, microbiology, and neuroradiology to learn what was going on and to see how we could better help our patients."

Recognizing a Familiar Symptom

The medical term for COVID brain is encephalopathy. Members of MSK's Department of Neurology felt well-poised to study it, Dr. Wilcox says, because they are already used to treating the condition in other systemic inflammatory syndromes. It is a side effect in patients who are receiving a type of immunotherapy called chimeric antibody receptor (CAR) T cell therapy, a treatment for blood cancer. When CAR T cell therapy is given, it causes immune cells to release molecules called cytokines, which help the body to kill the cancer. But cytokines can seep into the area around the brain and cause inflammation.

When the MSK team first began studying COVID brain, though, they didn't know that cytokines were the cause. They first suspected that the virus itself was having an effect on the brain. The study in the Cancer Cell paper focused on 18 patients who were hospitalized at MSK with COVID-19 and were experiencing severe neurologic

problems. The patients were given a full neurology workup, including brain scans like MRIs and CTs and electroencephalogram (EEG) monitoring, to try to find the cause of their delirium. When nothing was found in the scans that would explain their condition, the researchers thought the answer might lie in the cerebrospinal fluid.

MSK's microbiology team devised a test to detect the COVID-19 virus in the fluid. Thirteen of the 18 patients had spinal taps to look for the virus, but it was not found. At that point, the rest of the fluid was taken to the lab of MSK physician-scientist Adrienne Boire for further study.

Using Science to Ask Clinical Questions

Jan Remsik, a research fellow in Dr. Boire's lab in the Human Oncology and Pathogenesis Program and the paper's other first author, led the analysis of the fluid. "We found that these patients had persistent inflammation and high levels of cytokines in their cerebrospinal fluid, which explained the symptoms they were having," Dr. Remsik says. He adds that some smaller case studies with only a few patients had reported similar findings, but this study is the largest one so far to look at this effect.

"We used to think that the nervous system was an immune-privileged organ, meaning that it didn't have any kind of relationship at all with the immune system," Dr. Boire says. "But the more we look, the more we find connections between the two." One focus of Dr. Boire's lab is studying how immune cells are able to cross the blood-brain barrier and enter this space, an area of research that's also important for learning how cancer cells are able to spread from other parts of the body to the brain.

"One thing that was really unique about Jan's approach is that he was able to do a really broad molecular screen to learn what was going on," Dr. Boire adds. "He took the tools that we use in cancer biology and applied them to COVID-19."

The inflammatory markers found in the COVID-19 patients were similar, but not identical, to those seen in people who have received CAR T cell therapy. And as with CAR T cell therapy, the neurologic effects are sometimes delayed. The initial inflammatory response with CAR T cell treatment is very similar to the reaction called cytokine storm that's often reported in people with COVID-19, Dr. Wilcox explains. With both COVID-19 and CAR T cell therapy, the neurologic effects come days or weeks later. In CAR T cell patients, neurologic symptoms are treated with steroids, but doctors don't yet know the role of anti-inflammatory treatments for people with neurologic symptoms of COVID-19. "Many of them are already getting steroids, and it's possible they may be benefitting," Dr. Wilcox says.

"This kind of research speaks to the cooperation across the departments at MSK and the interdisciplinary work that we're able to do," Dr. Boire concludes. "We saw people getting sick, and we were able to use our observations to ask big clinical questions and then take these questions into the lab to answer them."

Dr. Boire is an inventor on a patent related to modulating the permeability of the blood-brain barrier and is an unpaid member of the scientific advisory board of EVREN Technologies.

This work was funded by National Institutes of Health grant P30 CA008748, the Pew Charitable Trusts, the Damon Runyon Cancer Research Foundation, and the Pershing Square Sohn Cancer Research Alliance GC239280. It was also supported by the American Brain Tumor Association Basic Research Fellowship, the Terri Brodeur Breast Cancer Foundation Fellowship, and the Druckenmiller Center for Lung Cancer Research.

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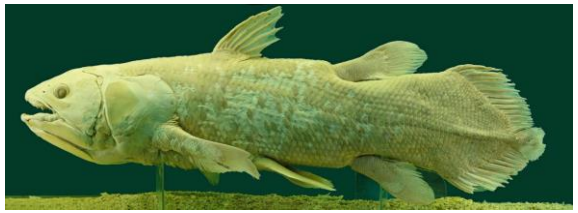
Not a living fossil: How the Coelacanth recently evolved dozens of new genes

Coelacanths gained 62 new genes from traveling DNA that was passed on from other species, new research reveals in a remarkable glimpse into how the genome of one of the most ancient and mysterious organisms evolved

The capture of the first living *Coelacanth*, a mighty ocean predator,

off the coast of South Africa caused quite a stir in 1938, 65 million years after its supposed extinction. It became known as a "living fossil" owing to its anatomy looking almost identical to the fossil record. But while the *Coelacanth*'s body may have changed little, its genome tells another story.



Coelacanths have an undeserved reputation as living fossils and the study adds to the growing body of research showing widespread evolution at the genome level. **Credit: Alberto Fernandez Fernandez via Wikimedia Commons**

Toronto scientists have now revealed that the African Coelacanth, *Latimeria chalumnae*, gained 62 new genes through encounters with other species 10 million years ago. Their findings are reported in the journal *Molecular Biology and Evolution*.

What's even more fascinating is how these genes came about. Their sequences suggest they arose from transposons, also known as "selfish genes". These are parasitic DNA elements whose sole purpose is to make more copies of themselves, which they sometimes achieve by moving between species.

The findings show the dramatic effect traveling transposon DNA can have on the creation of genes and provide a glimpse into some of the forces that shaped the genome of one of the most ancient and mysterious organisms.

"Our findings provide a rather striking example of this phenomenon of transposons contributing to the host genome," says Tim Hughes, senior study author and a professor of molecular genetics in the Donnelly Centre for Cellular and Biomolecular Research at the University of Toronto.

"We don't know what these 62 genes are doing, but many of them encode DNA binding proteins and probably have a role in gene regulation, where even subtle changes are important in evolution," says Hughes, who is Canada Research Chair in Decoding Gene Regulation and John W. Billes Chair of Medical Research at the Temerty Faculty of Medicine at U of T.

Transposons are sometimes also called "jumping genes" because they switch location in the genome, thanks to a self-encoded enzyme that recognises and move its own DNA code via "cut and paste" mechanism. New copies can arise through serendipitous jumps during cell division when the whole genome is replicated.

Over time, the enzyme's code drifts into disrepair and the jumping ceases. But if the altered sequence confers even subtle selective advantage to the host, it can begin new life as a bona fide host gene.

There are myriad examples of transposon-derived genes across species, but the *Coelacanth* stands out for the sheer scale of it.

"It was surprising to see coelacanths pop out among vertebrates as having a really large number of these transposon-derived genes because they have an undeserved reputation of being a living fossil," says graduate student Isaac Yellan who spearheaded the study. "The *Coelacanth* may have evolved a bit more slowly but it is certainly not a fossil," he says.

Yellan made the discovery while looking for counterparts in other species of a human gene he was studying. He knew that the gene, CGGBP1, had arisen from a particular type of transposon in the common ancestor of mammals, birds and reptiles. It was named after the protein it encodes, which binds CGG-containing DNA sequences, but it was difficult to study partly because it has no counterpart in other commonly researched species, such as fruitfly.

After scanning all available genomes, Yellan was able to find related genes, but their distribution across species was patchy and not what you'd expect from common ancestry. In addition to the single CGGBP-like gene in all mammals, birds and reptiles, Yellan found copies in some, but not all, fish he looked at, as well as in lamprey, a primitive vertebrate, and a type of fungus. Worms,

molluscs, and most insects had none. And then there were 62 in the *Coelacanth*, whose genome became available in 2013.

With common ancestry ruled out, it appears instead that the transposons came into various lineages at different times by being carried between species through what is known as horizontal gene transfer.

"Horizontal gene transfer fuzzies up the picture of where the transposons came from but we know from other species that it can occur via parasitism," says Yellan. "The most likely explanation is that they were introduced multiple times throughout evolutionary history."

It remains unclear what the genes are doing but several lines of evidence point to a finely-tuned role in gene regulation. Computational modeling and test tube experiments established that the genes' products are proteins which bind unique sequence signatures on the DNA, suggests a role in gene expression, similar to the human counterpart. Furthermore, the genes are varyingly switched on across dozen or so *Coelacanth* organs for which data exist, suggesting finely-tuned roles that are tissue-specific.

Where the genes originally came from and what they're doing in the *Coelacanth* may well remain a mystery. Research specimens are only occasionally pulled up by fishing boats and it took until 1998 to discover the other known living species, *Latimeria menadoensis*, in an Indonesian fish market.

The species split before the new genes appeared, ruling them out from driving speciation. Still, they might have shaped the African Coelacanth we know today whose majestic armor of royal blue scales throws shade on its brownish-coloured relative, said Yellan noting that this is pure speculation.

Alas, we may never find out.

"The *Coelacanth*s are extremely rare," says Yellan. "And they're very good at hiding."

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A rough guide to pharma partnership deals

Coronavirus vaccines are driving unusual partnerships with a range of benefits

By Derek Lowe

We're seeing a lot of biopharma partnership deals in the current stage of the coronavirus research efforts. And while some of these are business as usual, some of them aren't. Here's a rough field guide to how these tend to work.

One standard type of deal is when a small company partners up with a larger one. That's generally because the smaller one has some compound, technique, or platform that they own, but that they don't have the resources to take forward. In this business, that often means the advent of human clinical trials. Those are never cheap, but in some therapeutic areas they can be disorientingly expensive, suitable for only the largest players to take on. Manufacturing is another area that most smaller companies will think hard about before investing in: you're taking on a lot of fixed costs and a lot of (immediately depreciating) equipment, in many cases for a product you haven't even property launched yet.

It can be a better use of the money to have someone else deal with all that (and the packaging, shipping and so on). Even further downstream is the sales force, and while persuading people and organisations to buy them is not really a consideration with coronavirus vaccines, it's very much something to think about under more normal conditions.

Most of the time both partners have something the other one needs

It's easy to imagine that the smaller companies get the worst of such agreements ('So, you need a deal really bad? Here's a really bad deal!'). That's generally not the case. Most of the time both partners have something the other one needs, and terms are reached

that everyone considers worthwhile. Larger companies will also do deals with each other, of course. Sometimes this is to share the risk in a huge, expensive therapeutic area such as cardiovascular disease, and sometimes it's one company selling off an asset that no longer fits how they would like to allocate their money and time (they might, for example, have decided to get out of a whole therapeutic area entirely).

So when a BioNTech partners with a company like Pfizer on a vaccine, you can see what each of them bring to the proverbial table. But the recently announced partnership between the two of them and Sanofi, for manufacturing of that vaccine in Europe, is a bit unusual. Sanofi is of course a major player in vaccines itself, and they have been working with GlaxoSmithKline on a candidate of their own. In that case, GSK is bringing some powerful adjuvants to the deal, which Sanofi's recombinant proteins (like anyone's) are almost certain to need. But they've run into difficulties: the first look at immunogenicity in human trials showed an inadequate response, especially in older patients, adjuvant and all.

It would be pointless to get someone up to speed if they could only deliver an extra 10,000 vials

So Sanofi finds itself with some excess capacity for manufacturing and packaging, and they're a big enough player to (first) take on the technological challenge of dealing with the unusual lipid-nanoparticle formulation of the mRNA vaccines and their low-temperature handling, and (second) to make a real difference in the number of doses delivered. It would be pointless to get someone up to speed if they could only deliver an extra 10,000 (or 100,000) vials; the time and effort spent on that would be better used somewhere else.

The financial terms haven't been disclosed, but you could look at this as a marriage of convenience, under emergency conditions. You probably wouldn't see this under normal conditions, and you certainly wouldn't see it done with this sort of alacrity, either.

Will we see more of this sort of thing? Don't rule it out. The coronavirus variants that are spreading now mean that we may need some new vaccine versions to deal with them as booster shots or outright replacements. While that's feasible, especially with the mRNA platforms and the recombinant protein ones such as Novavax, it could easily lead to a manufacturing pinch if companies have to restart production. I wouldn't be surprised to see more of these sudden agreements if it comes to that. Let's all hope it doesn't, but let's also be glad that such options are available if we need them!

https://go.nature.com/3aa5F1Z

Nimble coronaviruses could leap straight from bats to humans

Some coronaviruses found in bats could jump directly to people without the need for further evolution in an intermediate animal host.

Victor Garcia at the University of North Carolina at Chapel Hill and his colleagues implanted mice with human lung tissue and infected the tissue with various coronaviruses, including SARS-CoV-2 and two closely related coronaviruses isolated from bats. All of the viruses could efficiently multiply in the lung tissue (A. Wahl *et al*. *Nature* https://doi.org/10.1038/s41586-021-03312-w; 2021). The findings suggest that coronaviruses circulating in bats could directly infect people, and have the potential to cause the next pandemic.

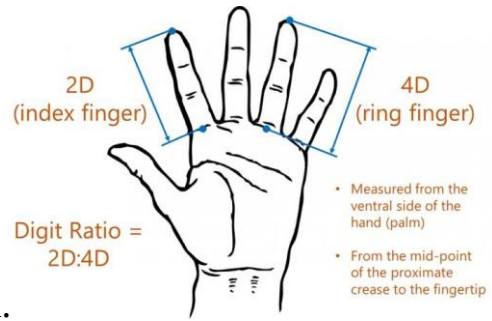
The researchers also used the animal model to show that an oral antiviral drug known as EIDD-2801 could significantly reduce infectious particles of SARS-CoV-2 in the lung tissue. They say that the drug, currently in late-stage clinical trials, could be used to prevent disease as well as to treat people within a day or two of exposure to SARS-CoV-2.

http://bit.ly/3ab6s2C

Children's finger length points to mothers' income level

- links with diseases that begin in the womb

Low-income mothers feminize their children in the womb by adjusting their hormones, whereas high-income mothers masculinize their children, a major study based on finger length, led by a Swansea University expert, has found.



The phenomenon is an unconscious evolutionary response aimed at boosting their offspring's chances of successful reproduction.

Low-income mothers feminize their children in the womb by adjusting their hormones, whereas high-income mothers masculinize their children, a major study based on finger length, led by a Swansea University expert, has found. The study was based on the relationship between the length of a person's index and ring fingers, known as the 2D:4D ratio. What is significant about the new report is that the team examined the ratio in relation to parental income. **John Manning, Swansea University**

It helps, in part, explain associations between low income, low levels of testosterone before birth, and major causes of mortality such as cardiovascular disease.

The study was based on the relationship between the length of a person's index and ring fingers, known as the 2D:4D ratio. A longer ring finger is a marker of higher levels of testosterone, whereas a longer index finger is a marker of higher levels of oestrogen. Generally, men have longer ring fingers, whereas women have longer index fingers.

The 2D:4D ratio is a widely-debated measure that has been the subject of over 1000 studies, but what is significant about the new report is that the team examined the ratio in relation to parental income.

Led by Professor John Manning of Swansea University, with colleagues in Austria and Jamaica, the team tested a hypothesis about evolutionary influences on the mother and her children. This suggests that for higher-income mothers, sons have higher reproductive success compared to daughters. For lower-income mothers, in contrast, daughters will be more reproductively successful. Known as the Trivers-Willard hypothesis, its senior author, Professor Robert Trivers, was also involved in this new study.

The team used data from over 250,000 people from around 200 countries, who were taking part in an online BBC survey. Participants were asked to measure their index and ring fingers and given instructions on how to do this accurately. They were also asked to indicate their parents' income level.

The results showed:

- ***Children of parents of above-average income had a low 2D:4D ratio, with longer ring fingers, which indicates high testosterone and low oestrogen before birth, hallmarks of a more masculinized foetus***
- ***Conversely, the children of parents of below-average income had a high 2D:4D ratio with longer index fingers, which indicates lower testosterone and higher oestrogen before birth, markers of a more feminized foetus***
- ***These effects were present for both men and women***

Professor John Manning of Swansea University's A-STEM research team in sport science, lead researcher on the study, said:

"Our results show that mothers with high income may secrete high levels of testosterone relative to oestrogen early in pregnancy, thereby masculinizing their male and female children. In contrast, women with low income may secrete low levels of testosterone, which will feminize their male and female children.

This is an evolutionary response, which mothers will not be aware of, let alone able to control. It is geared towards giving their

offspring the best chance of reproductive success.

For high-income mothers, the advantages of high testosterone for their sons are likely to outweigh its disadvantages for their daughters. For low-income mothers, the fitness gain from feminized daughters is likely to outweigh the fitness loss for feminized sons. This pattern is consistent with the Trivers-Willard hypothesis."

Professor Manning explained how the findings could shed light on susceptibility to disease: "These patterns suggest important effects on public health which are linked to poverty.

Low testosterone and high oestrogen in male foetuses may predispose those men, as adults, to diseases linked to poverty such as heart attacks, strokes, and high blood pressure.

It is well known that poverty is closely associated with poorer health. What our research indicates is that this link can be replicated across generations".

The study is in the Journal of Biosocial Sciences, published by Cambridge University Press.

http://bit.ly/3pbObGr

Coffee lovers, rejoice! Drinking more coffee associated with decreased heart failure risk

Circulation: Heart Failure Journal Report

Dallas - Dietary information from three large, well-known heart disease studies suggests drinking one or more cups of caffeinated coffee may reduce heart failure risk, according to research published today in *Circulation: Heart Failure*, an American Heart Association journal.

Coronary artery disease, heart failure and stroke are among the top causes of death from heart disease in the U.S. "While smoking, age and high blood pressure are among the most well-known heart disease risk factors, unidentified risk factors for heart disease remain," according to David P. Kao, M.D., senior author of the study, assistant professor of cardiology and medical director at the Colorado Center for Personalized Medicine at the University of Colorado School of Medicine in Aurora, Colorado.

"The risks and benefits of drinking coffee have been topics of ongoing scientific interest due to the popularity and frequency of consumption worldwide," said Linda Van Horn, Ph.D., R.D., professor and Chief of the Department of Preventive Medicine's Nutrition Division at the Northwestern University Feinberg School of Medicine in Chicago, and member of the American Heart Association's Nutrition Committee. "Studies reporting associations with outcomes remain relatively limited due to inconsistencies in diet assessment and analytical methodologies, as well as inherent problems with self-reported dietary intake."

Kao and colleagues used machine learning through the American Heart Association's Precision Medicine Platform to examine data from the original cohort of the Framingham Heart Study and referenced it against data from both the Atherosclerosis Risk in Communities Study and the Cardiovascular Health Study to help confirm their findings. Each study included at least 10 years of follow-up, and, collectively, the studies provided information on more than 21,000 U.S. adult participants.

To analyze the outcomes of drinking caffeinated coffee, researchers categorized consumption as 0 cups per day, 1 cup per day, 2 cups per day and ≥3 cups per day. Across the three studies, coffee consumption was self-reported, and no standard unit of measure were available.

The analysis revealed:

- ***In all three studies, people who reported drinking one or more cups of caffeinated coffee had an associated decreased long-term heart failure risk.***
- ***In the Framingham Heart and the Cardiovascular Health studies, the risk of heart failure over the course of decades decreased by 5-to-12% per cup per day of coffee, compared with no coffee consumption.***

- ***In the Atherosclerosis Risk in Communities Study, the risk of heart failure did not change between 0 to 1 cup per day of coffee; however, it was about 30% lower in people who drank at least 2 cups a day.***
- ***Drinking decaffeinated coffee appeared to have an opposite effect on heart failure risk - significantly increasing the risk of heart failure in the Framingham Heart Study. In the Cardiovascular Health Study however; there was no increase or decrease in risk of heart failure associated with drinking decaffeinated coffee. When the researchers examined this further, they found caffeine consumption from any source appeared to be associated with decreased heart failure risk, and caffeine was at least part of the reason for the apparent benefit from drinking more coffee.***

"The association between caffeine and heart failure risk reduction was surprising. Coffee and caffeine are often considered by the general population to be 'bad' for the heart because people associate them with palpitations, high blood pressure, etc. The consistent relationship between increasing caffeine consumption and decreasing heart failure risk turns that assumption on its head," Kao said. "However, there is not yet enough clear evidence to recommend increasing coffee consumption to decrease risk of heart disease with the same strength and certainty as stopping smoking, losing weight or exercising."

According to the federal dietary guidelines, three to five 8-ounce cups of coffee per day can be part of a healthy diet, but that only refers to plain black coffee. The American Heart Association warns that popular coffee-based drinks such as lattes and macchiatos are often high in calories, added sugar and fat. In addition, despite its benefits, research has shown that caffeine also can be dangerous if consumed in excess. Additionally, children should avoid caffeine. The American Academy of Pediatrics recommends that, in general, kids avoid beverages with caffeine.

"While unable to prove causality, it is intriguing that these three studies suggest that drinking coffee is associated with a decreased risk of heart failure and that coffee can be part of a healthy dietary pattern if consumed plain, without added sugar and high fat dairy products such as cream," said Penny M. Kris-Etherton, Ph.D., R.D.N., immediate past chairperson of the American Heart Association's Lifestyle and Cardiometabolic Health Council Leadership Committee, Evan Pugh University Professor of Nutritional Sciences and distinguished professor of nutrition at The Pennsylvania State University, College of Health and Human Development in University Park. "The bottom line: enjoy coffee in moderation as part of an overall heart-healthy dietary pattern that meets recommendations for fruits and vegetables, whole grains, low-fat/non-fat dairy products, and that also is low in sodium, saturated fat and added sugars. Also, it is important to be mindful that caffeine is a stimulant and consuming too much may be problematic - causing jitteriness and sleep problems."

Study limitations that may have impacted the results of the analysis included differences in the way coffee drinking was recorded and the type of coffee consumed. For example, drip, percolated, French press or espresso coffee types; origin of the coffee beans; and filtered or unfiltered coffee were details not specified. There also may have been variability regarding the unit measurement for 1 cup of coffee (i.e., how many ounces per cup). These factors could result in different caffeine levels. In addition, researchers caution that the original studies detailed only caffeinated or decaffeinated coffee, therefore these findings may not apply to energy drinks, caffeinated teas, soda and other food items with caffeine including chocolate.

The American Heart Association Precision Medicine Platform was used for data analysis of this study; it is a research hub with cloud-based workspaces, machine learning and artificial intelligence tools that enable high-performance computing, analytics and collaboration.

Co-authors are Laura M. Stevens, B.S., Ph.D. candidate; Erik Linstead, Ph.D.; and

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Jennifer Hall, Ph.D., is the chief of data science and the co-director of the Institute for Precision Cardiovascular Medicine at the American Heart Association. Laura M. Stevens, B.S., Ph.D. candidate, is a data scientist for the Institute for Precision Cardiovascular Medicine at the American Heart Association. Other author disclosures are in the manuscript.
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http://nyti.ms/3qq1A1M

Could a Single Vaccine Work Against All Coronaviruses?

Scientists are working on a shot that could protect against Covid-19, its variants, certain seasonal colds — and the next coronavirus pandemic.

By Carl Zimmer

The invention of Covid-19 vaccines will be remembered as a milestone in the history of medicine, creating in a matter of months what had before taken up to a decade. But Dr. Kayvon Modjarrad, the director of Emerging Infectious Diseases Branch at Walter Reed Army Institute of Research in Silver Spring, Md., isn't satisfied.

"That's not fast enough," he said. More than 2.3 million people around the world have died, and many countries will not have full access to the vaccines for another year or two: "Fast — truly fast — is having it there on day one."

There will be more coronavirus outbreaks in the future. Bats and other mammals are rife with strains and species of this abundant family of viruses. Some of these pathogens will inevitably spill over the species barrier and cause new pandemics. It's only a matter of time.

Dr. Modjarrad is one of many scientists who for years have been calling for a different kind of vaccine: one that could work against all coronaviruses. Those calls went largely ignored until Covid-19 demonstrated just how disastrous coronaviruses can be.

Now researchers are starting to develop prototypes of a so-called pancoronavirus vaccine, with some promising, if early, results from experiments on animals. Dr. Eric Topol, a professor of molecular medicine at the Scripps Research Institute in San Diego, thinks scientists should join together in another large-scale vaccine-creation project immediately.

"We have to get a real work force to accelerate this, so we can have it this year," he said. Dr. Topol and Dennis Burton, a Scripps immunologist, called for this project on broad coronavirus vaccines on Monday in the journal Nature.

After coronaviruses were first identified in the 1960s, they did not become a high priority for vaccine makers. For decades it seemed as if they only caused mild colds. But in 2002, a new coronavirus called SARS-CoV emerged, causing a deadly pneumonia called severe acute respiratory syndrome, or SARS. Scientists scrambled to make a vaccine for it.

Since no one had made a coronavirus vaccine for humans before, there was a huge amount to learn about its biology. Eventually, researchers chose a target for immunity: a protein on the surface of the virus, called spike. Antibodies that stick to the spike can prevent the coronavirus from entering cells and stop an infection.

Public health officials in Asia and elsewhere did not wait for the invention of a SARS vaccine to get to work, however. Their quarantines and other efforts proved remarkably effective. In a matter of months, they wiped out SARS-CoV, with only 774 deaths along the way.

The danger of coronaviruses became even clearer in 2012, when a second species spilled over from bats, causing yet another deadly respiratory disease called MERS. Researchers started work on MERS vaccines. But some researchers wondered if making a new vaccine for each new coronavirus — what Dr. Modjarrad calls "the one bug, one drug approach" — was the smartest strategy. Wouldn't it be better, they thought, if a single vaccine could work

against SARS, MERS and any other coronavirus?

That idea went nowhere for years. MERS and SARS caused relatively few deaths, and were soon eclipsed by outbreaks of other viruses such as Ebola and Zika.

In 2016, Maria Elena Bottazzi, a virologist at Baylor College of Medicine, and her colleagues applied for support from the American government to develop a pancoronavirus vaccine, but did not receive it. “They said there’s no interest in pancorona,” Dr. Bottazzi recalled.

Her team even lost funding for developing a SARS vaccine after they showed that it worked in mice, was not toxic to human cells and could be manufactured at scale. A coronavirus that had disappeared from view simply wasn’t a top priority.

Without enough money to start clinical trials, the scientists stored their SARS vaccine in a freezer and moved on to other research. “It’s been a struggle,” Dr. Bottazzi said.

Dr. Matthew Memoli, a virologist at the National Institute of Allergy and Infectious Diseases, looks back at those decisions as an enormous blunder. “It’s a failure of our system of science,” he said. “Funders tend to chase after shiny objects.”

Three years later, a third dangerous coronavirus emerged: the SARS-CoV-2 strain that causes Covid-19. Although this virus has a much lower fatality rate than its cousins that cause SARS and MERS, it does a far better job of spreading from person to person, resulting in more than 106 million documented cases around the world and still climbing.

All the lessons that researchers had learned about coronaviruses helped them move quickly to make new vaccines for SARS-CoV-2. Dr. Bottazzi and her colleagues used the technology they had created to make SARS vaccines to make one for Covid-19, which is now in early clinical trials.

Other researchers used even newer methods to move faster. The German company BioNTech created a genetic molecule called messenger RNA that encoded the spike protein. Partnering with Pfizer, the companies received U.S. government authorization for their vaccine in just 11 months. The previous record for a vaccine, against mumps, was four years.

Although the Covid-19 pandemic is still far from over, a number of researchers are calling for preparations for the next deadly coronavirus.

“This has already happened three times,” said Daniel Hoft, a virologist at Saint Louis University. “It’s very likely going to happen again.”

Researchers at VBI vaccines, a Cambridge-based company, took a small step toward a pancoronavirus vaccine last summer. They created virus-like shells studded with spike proteins from the three coronaviruses that caused SARS, MERS and Covid-19.

When the researchers injected this three-spike vaccine into mice, the animals made antibodies that worked against all three coronaviruses.

Intriguingly, some of those antibodies could also latch onto a fourth human coronavirus that causes seasonal colds — even though that virus’s spike proteins were not included in the vaccine. The scientists have made this data public but have not yet published it in a scientific journal.

David Anderson, VBI’s chief scientific officer, said it was not clear why the vaccine worked this way. One possibility is that an immune cell presented with several versions of a protein at once doesn’t make antibodies against just one. Instead, it makes a compromise antibody that works against them all.

“You’re educating it,” Dr. Anderson said, although he cautioned that this was speculation for now.

Last month, Pamela Bjorkman, a structural biologist at Caltech, and her colleagues published a more extensive experiment with a

universal coronavirus vaccine in the journal Science. The researchers attached only the tips of spike proteins from eight different coronaviruses to a protein core, known as a nanoparticle. After injecting these nanoparticles into mice, the animals generated antibodies that could stick to all eight of the coronaviruses — and to four other coronaviruses that the scientists had not used in the vaccine.

Dr. Modjarrad is leading a team at Walter Reed developing another vaccine based on a nanoparticle studded with protein fragments. They anticipate starting clinical trials on volunteers next month. Although the vaccine currently uses protein fragments only from SARS-CoV-2 spikes, Dr. Modjarrad and his colleagues are preparing to retool it as a pancoronavirus vaccine.

Dr. Hoft of Saint Louis University is working on a universal vaccine that does not rely on antibodies to the spike protein. Collaborating with Gritstone Oncology, a California-based biotech company, he has created a vaccine that prompts cells to make surface proteins that might alert the immune system as if a coronavirus — any coronavirus — were present. They are now preparing a clinical trial to see if it is effective against SARS-CoV-2. "We are interested to develop maybe a third-generation vaccine, which would be on the shelf and ready for the future outbreak," Dr. Hoft said.

Dr. Topol believes scientists should also explore another strategy: searching for pancoronavirus antibodies made by our own bodies during infections.

Researchers studying H.I.V. and other viruses have discovered, amid the billions of antibodies made during an infection, rare types that work against a huge range of related strains. It might be possible to create vaccines that coax the body to make abundant amounts of these broadly neutralizing antibodies.

Coronaviruses are similar enough to each other, Dr. Topol said, that it might not be that hard to build vaccines that make broadly neutralizing antibodies. "This is an easy family of viruses to take down," he said.

The search for a pancoronavirus vaccine may take longer than Dr. Topol's sunny expectations. But even if it takes a few years, it could help prepare the world for the next coronavirus that jumps the species barrier.

"I think we can have vaccines to prevent pandemics like this," Dr. Memoli said. "None of us wants to go through this again. And we don't want our children to go through this again, or our grandchildren, or our descendants 100 years from now."

Correction: *Feb. 10, 2021*

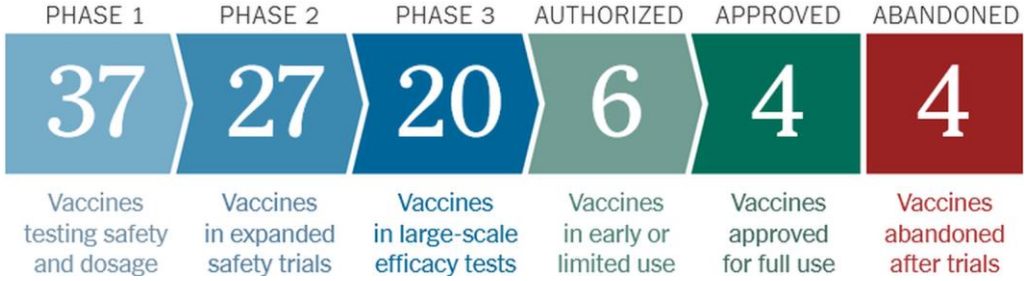
An earlier version of this article misstated which vaccine had the previous record for development speed. It was a shot for mumps, not chickenpox. The article also misspelled the name of a city. It is Silver Spring, not Silver Springs.

http://nyti.ms/3qruoUQ

Coronavirus Vaccine Tracker

A look at all the vaccines that have reached trials in humans.

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee



Vaccines typically require years of research and testing before reaching the clinic, but in 2020, scientists embarked on a race to produce safe and effective coronavirus vaccines in record time. Researchers are currently testing **69 vaccines** in clinical trials on humans, and 20 have reached the final stages of testing. At least 89 preclinical vaccines are under active investigation in animals.

New additions and recent updates	
Feb. 10	A vaccine from Italy's Takis and Rottapharm enters Phase 1.
Feb. 8	South Korea's SK Bioscience moves to Phase 1/2.
Feb. 7	South Africa halts plans for a rollout of AstraZeneca's vaccine.
Feb. 7	A second vaccine from Iran enters Phase 1.
Feb. 6	China gives conditional approval to the Sinovac vaccine.
Feb. 6	New York-based COVAXX moves to Phase 2.
Feb. 3	Vaxart stock plunges after a reported low antibody response.
Feb. 3	Mexico authorizes Russia's Sputnik V vaccine.
Feb. 2	Russia's Sputnik V vaccine has an efficacy of 91.6%.
Feb. 2	Cuba's Abdala vaccine moves to Phase 2.
Jan. 30	Hungary is the first E.U. country to authorize Sinopharm's vaccine.
Jan. 29	The E.U. authorizes the Oxford-AstraZeneca vaccine.
Jan. 29	Johnson & Johnson reports lower efficacy data in South Africa.
Jan. 28	Novavax reports lower efficacy data in South Africa.

Below is a list of all vaccines that have reached trials in humans, along with a selection of promising vaccines being tested in animals. For an explanation of virus variants and mutations, see our Coronavirus Variant Tracker. For treatments for Covid-19, see our Coronavirus Drug and Treatment Tracker. For an explanation of leading vaccines, see *How Nine Covid-19 Vaccines Work*.

Leading vaccines

Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	23	Approved in several countries. Emergency use in U.S., E.U., other countries.
Moderna	mRNA	3	Approved in Switzerland. Emergency use in U.S., U.K., E.U., others.
Gamaleya	Ad26, Ad5	3	Early use in Russia. Emergency use in other countries.
Oxford-AstraZeneca	ChAdOx1	23	Emergency use in U.K., E.U., other countries.
CanSino	Ad5	3	Limited use in China.
Johnson & Johnson	Ad26	3	
Vector Institute	Protein	3	Early use in Russia.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in Egypt, other coutries.
Sinovac	Inactivated	3	Approved in China. Emergency use in Brazil, other countries.
Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India.

The Vaccine Testing Process

The development cycle of a vaccine, from lab to clinic.

PRECLINICAL TESTING: Scientists test a new vaccine on cells and then give it to **animals** such as mice or monkeys to see if it produces an immune response.

PHASE 1 SAFETY TRIALS: Scientists give the vaccine to a **small number of people** to test safety and dosage, as well as to confirm that it stimulates the immune system.

PHASE 2 EXPANDED TRIALS: Scientists give the vaccine to **hundreds of people** split into groups, such as children and the elderly, to see if the vaccine acts differently in them. These trials further test the vaccine's safety.

PHASE 3 EFFICACY TRIALS: Scientists give the vaccine to **thousands of people** and wait to see how many become infected, compared with volunteers who received a placebo. These trials can determine if the vaccine protects against the coronavirus, measuring what's known as the efficacy rate. Phase 3 trials are also large enough to reveal evidence of relatively rare side effects.

EARLY OR LIMITED APPROVAL: Many countries have given emergency authorization based on preliminary evidence that they are safe and effective. China, Russia and other countries have begun administering vaccines before detailed Phase 3 trial data has been made public. Experts have warned of serious risks from jumping ahead of these results.

APPROVAL: Regulators review the complete trial results and plans for a vaccine's manufacturing, and decide whether to give it full approval.

COMBINED PHASES: One way to accelerate vaccine development is to

combine phases. Some vaccines are now in Phase 1/2 trials, for example, which this tracker would count as both Phase 1 and Phase 2.

PAUSED or ABANDONED: If investigators observe worrying symptoms in volunteers, they can pause the trial. After an investigation, the trial may resume or be abandoned.

http://wb.md/3jJTH27

Prostate Drugs Tied to Lower Risk for Parkinson's

Certain drugs currently used to treat benign prostatic hyperplasia (BPH) may provide neuroprotection and delay or prevent the onset of Parkinson's disease, new research suggests.

Erik Greb

Treatment of BPH with terazosin (Hytrin), doxazosin (Cardura), or alfuzosin (Uroxatral), all of which enhance glycolysis, was associated with a lower risk of developing Parkinson's disease than patients taking a drug used for the same indication, tamsulosin (Flomax), which doesn't affect glycolysis.

"If giving someone terazosin or similar medications truly reduces their risk of disease, these results could have significant clinical implications for neurologists," Jacob E. Simmering, PhD, assistant professor of internal medicine at the University of Iowa in Iowa City, told *Medscape Medical News.*

There are few reliable neuroprotective treatments for Parkinson's disease, he said. "We can manage some of the symptoms, but we can't stop it from progressing. If a randomized trial finds the same result, this will provide a new option to slow progression of Parkinson's disease," Simmering said.

The pathogenesis of Parkinson's disease is heterogeneous, however, and not all patients may benefit from glycolysis-enhancing drugs, the investigators note. Future research will be needed to identify potential candidates for this treatment, and clarify the effects of these drugs, they write.

The findings were published online February 1 in *JAMA Neurology.*

Time-Dependent Effects

The major risk factor for Parkinson's disease is age, which is associated with impaired energy metabolism. Glycolysis is decreased among patients with Parkinson's, yet impaired energy metabolism has not been investigated widely as a pathogenic factor in the disease, the authors write.

Studies have indicated that terazosin increases the activity of an enzyme important in glycolysis. Doxazosin and alfuzosin have a similar mechanism of action and enhance energy metabolism. Tamsulosin, a structurally unrelated drug, has the same mechanism of action as the other three drugs, but does not enhance energy metabolism.

In this report, the researchers investigated the hypothesis that patients who received therapy with terazosin, doxazosin, or alfuzosin would have a lower risk of developing Parkinson's than patients receiving tamsulosin. To do that, they used healthcare utilization data from Denmark and the United States, including the Danish National Prescription Registry, the Danish National Patient Registry, the Danish Civil Registration System, and the Truven Health Analytics MarketScan database.

The investigators searched the records for patients who filled prescriptions for any of the four drugs of interest. They excluded any patients who developed Parkinson's within 1 year of starting medication. Because use of these drugs is rare among women, they included only men in their analysis.

They looked at patient outcomes beginning at one year after the initiation of treatment. They also required patients to fill at least two prescriptions before the beginning of follow-up. Patients who switched from tamsulosin to any of the other drugs, or vice versa, were excluded from analysis.

The investigators used propensity score matching to ensure that patients in the tamsulosin and terazosin/doxazosin/alfuzosin groups were similar in terms of their other potential risk factors. The

primary outcome was the development of Parkinson's disease.

They identified 52,365 propensity score-matched pairs in the Danish registries and 94,883 pairs in the Truven database. The mean age was 67.9 years in the Danish registries and 63.8 years in the Truven database, and follow-up was approximately 5 years and 3 years respectively. Baseline covariates were well balanced between cohorts.

Among Danish patients, those who took terazosin, doxazosin, or alfuzosin had a lower risk of developing Parkinson's vs those who took tamsulosin (hazard ratio [HR], 0.88). Similarly, patients in the Truven database who took terazosin, doxazosin, or alfuzosin had a lower risk of developing Parkinson's than those who took tamsulosin (HR, 0.63).

In both cohorts, the risk for Parkinson’s among patients receiving terazosin, doxazosin, or alfuzosin, compared with those receiving tamsulosin, decreased with increasing numbers of prescriptions filled. Long-term treatment with any of the three glycolysis-enhancing drugs was associated with greater risk reduction in the Danish (HR, 0.79) and in the Truven (HR, 0.46) cohorts, vs tamsulosin.

Differences in case definitions, which may reflect how Parkinson's disease was managed, complicate comparisons between the Danish and Truven cohorts, said Simmering. Another challenge is the source of the data.

"The Truven data set was derived from insurance claims from people with private insurance or Medicare supplemental plans," he told *Medscape Medical News*. "This group is quite large but may not be representative of everyone in the United States. We would also only be able to follow people while they were on one insurance plan. If they switched coverage to a company that doesn't contribute data, we would lose them."

The Danish database, however, includes all residents of Denmark. Only people who left the country were lost to follow-up.

The results support the hypothesis that increasing energy in cells slows disease progression, Simmering added. "There are a few conditions, mostly REM sleep disorders, that are associated with future diagnosis of Parkinson's disease. Right now, we don't have anything to offer people at elevated risk of Parkinson's disease that might prevent the disease. If a controlled trial finds that terazosin slows or prevents Parkinson's disease, we would have something truly protective to offer these patients."

Biomarker Needed

Commenting on the results, Alberto J. Espay, MD, MSc, professor of neurology at University of Cincinnati Academic Health Center, Cincinnati, Ohio, was cautious. "These findings are of unclear applicability to any particular patient without a biomarker for a deficit of glycolysis that these drugs are presumed to affect," Espay told *Medscape Medical News*. "Hence, there is no feasible or warranted change in practice as a result of this study."

Pathogenic mechanisms are heterogeneous among patients with Parkinson's disease, Espay added. "We will need to understand who among the large biological universe of Parkinson's patients may have impaired energy metabolism as a pathogenic mechanism to be selected for a future clinical trial evaluating terazosin, doxazosin, or alfuzosin as a potential disease-modifying intervention."

Parkinson's is not one disease, but a group of disorders with unique biological abnormalities, said Espay. "We know so much about 'Parkinson's disease' and next to nothing about the biology of individuals with Parkinson's disease."

This situation has enabled the development of symptomatic treatments, such as dopaminergic therapies, but failed to yield disease-modifying treatments, he said.

The University of Iowa contributed funds for this study. Simmering has received pilot funding from the University of Iowa Institute for Clinical and Translational Science. He had no conflicts of interest to disclose. Espay has disclosed no relevant financial

relationships.

JAMA Neurol. Published online February 1, 2021. Full text

http://nyti.ms/3tTVXIT

Childhood Colds Do Not Prevent Coronavirus Infection, Study Finds

New research casts doubt on the idea that prior infections with garden-variety coronaviruses might shield some people, particularly children, amid the pandemic.

By Apoorva Mandavilli

The theory was simple and compelling: Children are less vulnerable to the new coronavirus because they carry antibodies to other common coronaviruses that cause the common cold. The idea might also explain why some people infected with the new virus have mild symptoms while others — presumably without antibodies to common cold coronaviruses — are much more severely affected.

The notion gained traction particularly among people who claimed that this existing protection would swiftly bring human populations to herd immunity, the point at which a pathogen's spread slows to a halt as it runs out of hosts to infect. A study in the journal Science, published in December, gave the hypothesis a strong boost.

But for all its appeal, the theory does not hold up, according to a new study published on Tuesday in the journal Cell. Based on carefully conducted experiments with live virus and with hundreds of blood samples drawn before and after the pandemic, the new research refutes the idea that antibodies to seasonal coronaviruses have any impact on the new coronavirus, called SARS-CoV-2.

"Going into this study, we thought we would learn that individuals that had pre-existing, pre-pandemic antibodies against SARS-CoV-2 would be less susceptible to infection and have less severe Covid-19 disease," said Scott Hensley, an immunologist at the University of Pennsylvania. "That's not what we found."

He and his colleagues concluded that most people are exposed to seasonal coronaviruses by age 5. As a result, about one in five people carries antibodies that recognize the new coronavirus.

But these antibodies are not neutralizing — they cannot disarm the virus, nor do they mitigate the severity of symptoms following infection, the team found.

The researchers also compared antibodies to common cold coronaviruses in children and adults and found no difference in the amounts. By contrast, the study in Science had reported that about 5 percent of adults carried those antibodies, compared with 43 percent of children.

That study "reported very high levels of pre-pandemic cross-reactive neutralizing antibodies in kids, something that we did not find," Dr. Hensley said. ("Cross-reactive" refers to antibodies able to attack similar sites on more than one type of virus.)

"I don't have an explanation for the difference from the Science study, honestly," he added.

Perhaps the difference in locations — Pennsylvania, in his study, versus Britain in the previous research — may explain some of the discrepancy, he said.

Other experts said they found Dr. Hensley's study to be more convincing of the two and more consistent with circumstances in which large groups of people become infected with the new coronavirus.

For example, a single person infected with the new coronavirus at a Wisconsin summer camp set off an outbreak that affected 76 percent of the other attendees, noted John Moore, a virologist at Weill Cornell Medicine in New York.

Similarly, on a fishing trawler that left for sea from Seattle, only three sailors who had antibodies to the new coronavirus before the trip stayed virus-free. Those are not the infection rates you would see if protective antibodies were widely distributed in the population, Dr. Moore said.

"The idea that having the snuffles a while back somehow protects you from SARS-CoV-2 infection has always left me cold, but it's been a persistent urban legend throughout the pandemic," he said. "Hopefully, this new paper will finally cool everyone down and put such thoughts into the freezer."

Experts also praised the new study's careful and rigorous approach.

"It's really nice to have a study that's this well done," said Shane Crotty, a virologist at the La Jolla Institute of Immunology in San Diego.

The theory that existing antibodies can protect people from the new virus "has definitely got a strong appeal because at first blush, it can explain a lot of the pandemic," Dr. Crotty said. "But a beautiful idea doesn't make it true."

Dr. Hensley and his colleagues examined samples from 251 people who had donated blood to the University of Pennsylvania before the pandemic and then went on to develop Covid-19.

Those people carried levels of antibodies able to recognize the new coronavirus that were no different from those seen in blood samples drawn from 251 people who remained uninfected. And the levels showed no relationship to the clinical outcome in any of the patients.

"It's hard to come by those kinds of samples — I was just impressed," said Marion Pepper, an immunologist at the University of Washington in Seattle. "It's like three different studies wrapped into one."

The most important part of the coronavirus is the spike protein on its surface, which docks onto human cells. The spike is also the most distinctive part of the virus, so it makes sense that antibodies to seasonal viruses would be unlikely to recognize and disarm it, Dr. Pepper said. "There are very specific parts of these viruses that are critical for infection, and most of this cross-reactivity isn't directed to those parts," she said.

But George Kassiotis, an immunologist at the Francis Crick Institute in London who led the study published in Science, disagreed with the conclusions of the new research. It "largely confirms rather than contradicts our main findings," he said, adding that the new study was too small to rule out any role for existing antibodies.

But even if people really were carrying coronavirus antibodies from childhood infections, the protection they confer is not powerful enough to matter, said Jesse Bloom, an evolutionary biologist at the Fred Hutchinson Cancer Research Center in Seattle.

"If there is no effect that is measurable in a study with hundreds of people in both the infected and uninfected groups, then the effect is certainly tiny," Dr. Bloom said.

Most of the vaccines developed for the new coronavirus are focused on the spike protein. Some scientists have argued that antibodies to other parts of the virus may also be critical to protection. But the new study suggests that the other antibodies are of minimal importance in protecting people from SARS-CoV-2.

The experts all said the new study did not rule out a role for immune cells, called memory B cells and T cells, produced in response to seasonal coronaviruses. Those cells might recognize some parts of the new virus and attack it, easing the severity of symptoms.

Still, the cells would not prevent infection, Dr. Crotty said. When exposed to the new virus, the immune cells might be roused "fast enough that you would have an asymptomatic infection that you never noticed," he said. "But no, they wouldn't stop infection."

Tests of T cells are laborious and expensive, so analyses of their contribution to immunity are not yet complete. In the meantime, the new study at least rules out a significant role for existing antibodies, Dr. Hensley said: "We've sort of written one chapter here, but there's still so much to be learned."

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Definitely not the flu: risk of death from COVID-19 3.5 times higher than from flu

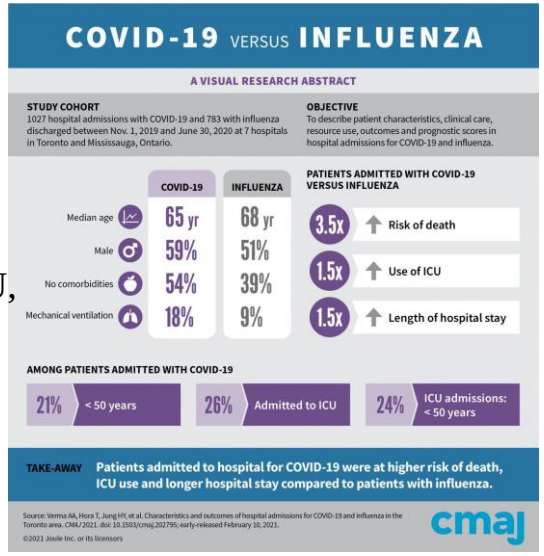
We can now say definitively that COVID-19 is much more severe than seasonal influenza

A new study published in *CMAJ (Canadian Medical Association Journal*) found that the risk of death from COVID-19 was 3.5 times higher than from influenza.

"We can now say definitively that COVID-19 is much more severe than seasonal influenza," says Dr. Amol Verma, St. Michael's Hospital, Unity Health Toronto, and the University of Toronto.

"Patients admitted to hospital in Ontario with COVID-19 had a 3.5 times greater risk of death, 1.5 times greater use of the ICU, and 1.5 times longer hospital stays than patients admitted with influenza."

These findings are similar to study results recently reported in France and the United States.



Risk of death from COVID-19 3.5 times higher than flu **Credit: CMAJ**

The study compared hospitalizations for influenza between November 1, 2019, and June 30, 2020, in 7 large hospitals in Toronto and Mississauga -- areas with large populations and high levels of COVID-19. It included all patients admitted to medical services or the intensive care unit (ICU) for influenza or COVID-19. There were 783 hospitalizations for influenza in 763 unique patients compared with 1027 hospitalizations for COVID-19 in 972 unique patients (representing 23.5% of all hospitalizations for COVID-19 in Ontario during the study period).

Most patients hospitalized with COVID-19 had few other illnesses, and 21% were younger than 50 years of age. People younger than 50 also accounted for almost 1 in 4 (24%) admissions to the ICU.

"Many people believe that COVID-19 mainly affects older people," says Dr. Verma. "It is true that COVID-19 affects older adults most severely. We found that among adults over 75 years who were hospitalized with COVID-19, nearly 40% died in hospital. But it can also cause very serious illness in younger adults. Adults under 50 accounted for 20% of all COVID-19 hospitalizations in the first wave of the pandemic. Nearly 1 in 3 adults younger than 50 hospitalized with COVID-19 required intensive care, and nearly 1 in 10 required an unplanned readmission to hospital after discharge."

People hospitalized for COVID-19 had greater use of the ICU, were more likely to be put on a ventilator and had longer hospital stays than people with influenza.

"These differences may be magnified by low levels of immunity to the novel coronavirus compared with seasonal influenza, which results from past infections and vaccination," says Dr. Verma. "Hopefully, the severity of COVID-19 will decrease over time as people are vaccinated against the virus and more effective treatments are identified. There is, unfortunately, also the possibility that variants of the virus could be even more severe."

"Characteristics and outcomes of hospital admissions for COVID-19 and influenza in the Toronto area" is published February 10, 2021.

http://bit.ly/3aZKxKV

'Farfarout'! Solar system's most distant planetoid confirmed

Planetoid nicknamed "Farfarout" is almost four times farther from the Sun than Pluto

A team, including an astronomer from the University of Hawai'i

Institute for Astronomy (IfA), have confirmed a planetoid that is almost four times farther from the Sun than Pluto, making it the most distant object ever observed in our solar system. The planetoid, nicknamed "Farfarout," was first detected in 2018, and the team has now collected enough observations to pin down the orbit. The Minor Planet Center has now given it the official designation of 2018 AG37.

Farfarout's name distinguished it from the previous record holder "Farout," found by the same team of astronomers in 2018. The team includes UH Mānoa's David Tholen, Scott S. Sheppard of the Carnegie Institution for Science, and Chad Trujillo of Northern Arizona University, who have an ongoing survey to map the outer solar system beyond Pluto.

Journey around the Sun

Farfarout's current distance from the Sun is 132 astronomical units (au); 1 au is the distance between the Earth and Sun. For comparison, Pluto is only 34 au from the Sun. The newly discovered object has a very elongated orbit that takes it out to 175 au at its most distant, and inside the orbit of Neptune, to around 27 au, when it is closest to the Sun.

Farfarout's journey around the Sun takes about a thousand years, crossing the giant planet Neptune's orbit every time. This means Farfarout has probably experienced strong gravitational interactions with Neptune over the age of the solar system, and is the reason why it has such a large and elongated orbit.

"A single orbit of Farfarout around the Sun takes a millennium," said Tholen. "Because of this long orbital period, it moves very slowly across the sky, requiring several years of observations to precisely determine its trajectory."

Discovered on Maunakea

Farfarout will be given an official name after its orbit is better determined over the next few years. It was discovered at the Subaru 8-meter telescope located atop Maunakea in Hawai'i, and recovered using the Gemini North and Magellan telescopes in the past few years to determine its orbit based on its slow motion across the sky.

Farfarout is very faint, and based on its brightness and distance from the Sun, the team estimates its size to be about 400 km across, putting it on the low end of being a dwarf planet, assuming it is an ice-rich object.

"The discovery of Farfarout shows our increasing ability to map the outer solar system and observe farther and farther towards the fringes of our solar system," said Sheppard. "Only with the advancements in the last few years of large digital cameras on very large telescopes has it been possible to efficiently discover very distant objects like Farfarout. Even though some of these distant objects are quite large, being dwarf planet in size, they are very faint because of their extreme distances from the Sun. Farfarout is just the tip of the iceberg of solar system objects in the very distant solar system."

Interacting with Neptune

Because Neptune strongly interacts with Farfarout, its orbit and movement cannot be used to determine if there is another unknown massive planet in the very distant solar system, since these interactions dominate Farfarout's orbital dynamics. Only those objects whose orbits stay in the very distant solar system, well beyond Neptune's gravitational influence, can be used to probe for signs of an unknown massive planet. These include Sedna and 2012 VP113, which, although they are currently closer to the Sun than Farfarout (at around 80 au), they never approach Neptune and thus would be most influenced by the possible Planet X instead.

"Farfarout's orbital dynamics can help us understand how Neptune formed and evolved, as Farfarout was likely thrown into the outer solar system by getting too close to Neptune in the distant past," said Trujillo. "Farfarout will likely interact with Neptune again

since their orbits continue to intersect."

http://bit.ly/3dbjZcu

18,000-year-old seashell is the oldest manmade wind instrument of its type

A large shell is the oldest wind instrument of its type

Almost 80 years after its discovery, a large shell from the ornate Marsoulas Cave in the Pyrenees has been studied by a multidisciplinary team from the CNRS, the Muséum de Toulouse, the Université Toulouse—Jean Jaurès and the Musée du quai Branly—Jacques-Chirac. They believe it is the oldest wind instrument of its type. The scientists have revealed how it sounds in a study published in the journal *Science Advances* on 10 February 2021.

At 31 cm in height, 18 cm in diameter (at the widest point) and up to 0.8 cm thick, this conch, which bears witness to a colder sea, is thus larger and thicker than more recent ones. **Credit: © Carole Fritz et al. 2021.**

The Marsoulas Cave between Haute-Garonne and Ariège was the first decorated cave to be found in the Pyrenees. Discovered in 1897, the cave bears witness to the beginning of the Magdalenian culture in this region at the end of the Last Glacial Maximum. During an inventory of the material from the archaeological excavations, most of which is kept in the Muséum de Toulouse, the scientists examined a large Charonia lampas (sea snail) shell, which had been largely overlooked when discovered in 1931.

The tip of the shell is broken, forming a 3.5 cm diameter opening. As this is the hardest part of the shell, the break is clearly not accidental. At the opposite end, the shell opening shows traces of retouching (cutting) and a tomography scan has revealed that one of the first coils is perforated. Finally, the shell has been decorated with a red pigment, hematite, characteristic of the Marsoulas Cave, which indicates its status as a symbolic object.

To confirm the hypothesis that this conch was used to produce sounds, scientists enlisted the help of a horn player, who managed to produce three sounds close to the notes C, C-sharp and D.

Listen to the sound of the Marsoulas conch, as it may have been played 18,000 years ago**. Credit: © Carole Fritz et al. 2021 / playing: Jean-Michel Court / recording: Julien Tardieu**

As the opening was irregular and covered with an organic coating, the researchers assume that a mouthpiece was also attached, as is the case for more recent conches in collection of the Musée du quai Branly—Jacques Chirac. 3-D impressions of the conch will enable this lead to be explored and verify whether it can be used to produce other notes.

Reconstruction of the instrument being played. In the background, a red dotted buffalo decorates the walls of the Marsoulas Cave; similar motifs decorate the instrument. **© Carole Fritz et al. 2021 / drawing: Gilles Tosello**

The first carbon-14 dating of the cave, carried out on a piece of charcoal and a fragment of bear bone from the same archaeological level as the shell, provided a date of around 18,000 years. This makes the Marsoulas conch the oldest wind instrument of its type: To date, only flutes have been discovered in earlier European Upper Palaeolithic contexts; the conches found outside Europe are much more recent.

In addition to immersing us in the sounds produced by our Magdalenian ancestors, this shell reinforces the idea of exchanges between the Pyrenees and the Atlantic coast, more than 200 kilometers away.

More information: *Fritz el al., "First record of the sound produced by the oldest Upper*

Paleolithic seashell horn," Science Advances (2021). advances.sciencemag.org/lookup ... .1126/sciadv.abe9510

http://bit.ly/3tX9zCY

Genes in The Placenta Appear to Determine a Baby's Risk of Developing Schizophrenia

Scientists have zeroed in on the combination of risk factors that could predict which infants are at greatest risk

Mike McRae

After tracing the origins of schizophrenia to genes expressed in the placenta while in utero, scientists have now zeroed in on the combination of risk factors that could predict which infants are at greatest risk of developing the condition later in life.

The findings reinforce an emerging picture of schizophrenia as a genetic disorder, with a fate determined by complications that can arise during pregnancy.

Researchers from the Lieber Institute for Brain Development at Johns Hopkins University and the University of North Carolina in the US analysed the relationship between key genes and cognitive development in the first few years after birth.

"By identifying the specific genes activated in the placenta that appear to be unique for schizophrenia risk, we have zeroed in on a set of biological processes that could be targeted to improve placental health and reduce schizophrenia risk," says Daniel R. Weinberger, director of the Lieber Institute. "To date, prevention from early in life has seemed unapproachable if not unimaginable, but these new insights offer possibilities to change the paradigm."

While any possible prevention strategy remains far in the future, the study does inch us closer to understanding how genes determine the development of schizophrenia, and the impact pregnancy has on their expression.

Symptoms of the disorder don't usually appear until early adulthood, revealing itself in a variety of behaviours and symptoms.

In some, schizophrenia is experienced as confusion or disorganised thinking. In more serious cases it can manifest in hallucinations, impeded motor control, and delusions.

What makes the difference in severity, or even how the condition develops in the first place, is still a complete unknown.

Decades of research has resulted in a frustrating mix of clues. Studies on twins suggest for around four out of every five diagnoses, genes play a key role. Yet that still leaves roughly 20 percent of cases without an obvious basis in inheritance.

Population based studies have uncovered correlations between childhood illness, challenges before or shortly after birth, and even a potential role for the season we're born in.

Combining the evidence, it seems the genes we inherit can put us at a disadvantage should the environment our brain is developing within turn nasty at crucial moments.

Weinberger and his team demonstrated in 2018 roughly a third of the genes associated with schizophrenia were expressed by the placenta during complicated pregnancies – especially those with high blood pressure or resulted in a pre-term delivery.

Male infants, it seemed, were for some reason especially at risk of later developing schizophrenia.

Building on this research, the scientists looked again at the genes being expressed in the placenta during early-life complications, seeking correlations with other neurological disorders such as autism or signs of learning challenges. They found the genomic risk score for schizophrenia was a strong predictor of difficulties in cognitive development in infancy among adults with schizophrenia, as well as the relative size of their brain based on MRI scans.

But there was no indication that these genes predisposed the growing brain to any other conditions.

"Measuring schizophrenia genetic scores in the placenta combined with studying the first two years of cognitive developmental

patterns and early life complications could prove to be an important approach to identify those babies with increased risks," says Weinberger.

Having a high risk score isn't a diagnosis of schizophrenia in itself. Even with complications during pregnancy, other genetic environmental factors might compensate, nudging neurological development in other directions.

Brains are complex organs, after all, and we're still teasing apart the multitude of factors that can determine how they're wired.

But knowing there is a risk can help parents develop their own understanding of schizophrenia, and provide their family with the resources they need to help accommodate any possible challenges that come with the disorder.

Perhaps one day there will be options to reduce any negative impacts these 'schizophrenia genes' could have. "Understanding the trajectories leading to neurodevelopmental disorders is a big challenge, but a necessary one to design strategies aimed at prevention," says Weinberger. *This research was published in PNAS.*

http://bit.ly/37dytVf

'Game-Changer' Drug Promotes Weight Loss Like No Medicine Ever Seen, Scientists Say

Experimental treatment recently trialled by scientists could open new doors for treating obesity patients

Peter Dockrill

In the simplest terms, obesity is the product of a body's energy output being less than its energy input. But in reality, there's nothing simple about this complex and mysterious disease.

Obesity, which has skyrocketed in recent decades – now defining the body mass of over 40 percent of adult Americans – isn't just difficult for people to endure and scientists to understand. It's also incredibly hard to treat.

Beyond commitment to sustained lifestyle changes – healthy eating and exercise, effectively – there are really only two potential options that may help: bariatric surgery and weight-loss medications. The former is invasive and carries various risks and complications. As for the drugs, they don't always work, and can have their own adverse effects too.

However, an experimental treatment recently trialled by scientists and detailed in a study published this week could open new doors for treating obesity patients with a weight-loss drug.

In the study, which involved almost 2,000 obese adults across 16 different countries, participants took a weekly dose of a drug called semaglutide, an existing medication already used in the treatment of type 2 diabetes. A control group took only a placebo, in place of the medication. Both groups received a lifestyle intervention course designed to promote weight loss.

At the end of the trial, the participants who took the placebo lost a small but clinically insignificant amount of weight. But for those who took semaglutide, the effects were pronounced.

After 68 weeks of treatment with the drug – which suppresses appetite due to a variety of effects on the brain – participants taking semaglutide lost on average 14.9 percent of their body weight. And over 30 percent of the group lost more than 20 percent of their body weight. Broadly speaking, this makes the drug up to twice as effective as existing medications for weight loss, the researchers say, approaching the kind of efficacy of surgical interventions.

"No other drug has come close to producing this level of weight loss – this really is a game-changer," says obesity researcher Rachel Batterham from University College London. "For the first time, people can achieve through drugs what was only possible through weight-loss surgery."

In addition to losing weight, participants registered improvements in other areas, showing reductions in various cardiometabolic risk factors, and reporting quality of life improvements.

While the results are compelling, semaglutide dosage for anti-obesity effects does come with some drawbacks.

Mild-to-moderate effects were reported by many participants (in both the semaglutide and placebo groups), including nausea and diarrhoea. While the effects were temporary, they were enough for nearly 60 of participants to discontinue their treatment, compared with just five in the placebo group.

At present, the drug requires a weekly injection to work – whereas an oral form of the medicine would likely be preferred by patients.

More significantly, we don't yet have data on what happened to the participants after the drug regimen ceased at the end of the trial.

For at least one individual, however, who spoke to *The New York Times*, her weight began to creep up after the trial was over.

"While drugs like this may prove useful in the short term for obtaining rapid weight loss in severe obesity, they are not a magic bullet for preventing or treating less severe degrees of obesity," says nutritionist Tom Sanders, an emeritus professor at King's College London, who wasn't involved with the study. "Public health measures that encourage behavioural changes such as regular physical activity and moderating dietary energy intake are still needed."

Nobody would deny the wisdom of that, but if further analysis of semaglutide turns out to be positive, we could also be looking at an important new pharmaceutical option to help combat obesity.

And that option might arrive sooner than we think.

The study, funded by pharmaceutical company Novo Nordisk – which sells semaglutide as an anti-diabetic medication – is now being tendered as evidence to international health regulatory authorities, in support of an application to market the drug as an obesity treatment. The US FDA, along with its counterparts in the UK and Europe, is currently assessing the data.

The findings are reported in *The New England Journal of Medicine*.

http://nyti.ms/3tXZXrw

Whale Songs Could Reveal Deep Secrets Beneath the Oceans

The aquatic mammals' sound waves penetrate into the rocks under the waves, which could assist seismologists' surveys.

By Robin George Andrews

In 2019, Václav Kuna, a seismologist, was perusing recordings from dozens of seismometers at the bottom of the northeast Pacific Ocean, when he kept finding strange noises: one-second chirps, repeating every 30 seconds or so.

This staccato symphony turned out to be the songs of fin whales.

"Because I'm a seismologist, I wasn't just like, oh, fin whales, that's cute," said Dr. Kuna, then a doctoral student at Oregon State University.

He dove deeper into the data and found that these booming cetacean calls were impacting the seafloor. As they did, some of their energy transmitted through the ground as seismic waves, which bounced around the buried rocky expanse before being picked up by those ocean-bottom seismometers.

What Dr. Kuna, now at the Institute of Geophysics of the Czech Academy of Sciences, and John Nabelek of Oregon State would soon discover is that fin whale song can be used to peer into the oceanic crust. Using this biological source of seismicity, they found they could see 8,200 feet below the seafloor, through sediments and the underlying volcanic rock. There would be less need to wait for a tectonic source of seismic waves, or sending a fully crewed, air gun-armed ship into the middle of the ocean to create artificial seismicity and visualize the layer-cake nature of the planet's underworlds.

"It's a nice example of how we make use of the data the planet provides for us," said Jackie Caplan-Auerbach, a seismologist and volcanologist at Western Washington University not involved with

the work, which was published Thursday in Science.

Fin whales — 60-ton, 80-foot long, graceful beasts — get their name from the prominent fin on their backs. They are fast swimmers that love to eat krill, schools of tiny fish and squid. And as they swim in groups, they gossip with one another by making booming 189-decibel chirps.

"They're really loud," said William Wilcock, a marine geophysicist at the University of Washington who wasn't involved with the work. "They're nearly as loud as a big container ship."

Usually, whale song inconveniences seismologists. Like static on a telephone line, it creates interference that can obfuscate earthquake seismicity, requiring scientists to filter it out.

"For some of us, it's just been, 'ugh, these dang whales are in my data,'" Dr. Caplan-Auerbach said. Humpback whales have interrupted her research in the past on Lō'ihi Seamount, an underwater Hawaiian volcano. "We had tons and tons of whale song, and to me it was just total noise in my data."

But as this new study shows, this noise can be used to study the planet's interior. "And that's awesome," she said.

"It's never going to replace air guns," Dr. Kuna said. Fin whale seismic waves are somewhat weak, which means their imaging of the subsurface is of relatively low resolution. "But it is a complement. And it's free."

Although seismologists are careful to avoid marine life, a recent report detailed just how noisy the oceans have become in recent years as a result of human activity. Finding more ways to use fin whale seismology could mean adding less to the cacophony. "It's win-win," Dr. Kuna said.

For this study, the researchers had to determine the location of the fin whales, a bit like searching for the epicenter of an earthquake. They looked at the arrival times of both the whale chirps' sound waves heading directly to the seismometer and the sound waves ricocheting between the sea surface and the seafloor. The time difference revealed the whale's distance. Making some reasonable assumptions about the fin whale's typical swimming depth, they could trace their journeys through the ocean.

This paper may be about the seismological benefits of fin whales, but this method may prove useful to marine ecologists, Dr. Wilcock said. In recent years, seismometers on land have been trying to track elephants and estimate their populations. The same principle could apply to fin whales, animals endangered by climate change, habitat loss and the grim legacy of commercial whaling. And like those elephant-eavesdropping seismometers, machine learning may one day listen for signature fin whale songs and autonomously detect different pods of fin whales, or individuals within those groups.

"We can use the tools of biology to study seismology," Dr. Caplan-Auerbach said. "And we can use the tools of seismology to study biology."

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One dose of COVID-19 vaccine provokes strong immune response in those previously infected

Strong response detected regardless of duration between infection and vaccination; multi-ethnic groups exhibit similar response

Although clinical trial data are encouraging, real-world evidence with regard to the COVID-19 vaccine remains scarce. In particular, response to the vaccine among those previously infected with SARS-CoV-2 is still not completely understood.

Researchers from Bar-Ilan University and Ziv Medical Center now report preliminary evidence that people previously infected with the virus responded very strongly to one dose of the Pfizer vaccine, regardless of when they were infected and whether or not they had detectable antibodies against COVID-19 prior to receiving the vaccine.

Their study, published on February 11, 2021 in the journal *Eurosurveillance*, was conducted on a cohort of 514 staff members at Ziv Medical Center. Seventeen of them were infected with COVID-19 anytime between one and ten months before receiving the first dose of the vaccine. Antibody levels of the entire cohort were measured prior to vaccination and thereafter to determine response to the vaccine.

The response among those previously infected was so effective that it opens the debate as to whether one dose of the vaccine may suffice. "This finding can help countries make informed decisions regarding vaccine policy - for instance, whether those previously infected should be vaccinated in priority and, if so, with how many doses," says Prof. Michael Edelstein, of the Azrieli Faculty of Medicine of Bar-Ilan University, who led the study. "It also offers reassurance that not having detectable antibodies after being infected does not necessarily mean that protection following infection is lost."

The research also provided evidence that immune response was similar across multi-ethnic groups. Ziv Medical Center, where the study was conducted, is staffed by a workforce comprised of Jews, Arabs and Druze, among others. Members of each of these groups responded very similarly to the first dose of the vaccine, a welcome finding considering that the virus itself is known to affect some groups more than others.

The strong response to one dose of the vaccine among those previously infected regardless of the duration between infection and vaccination is good news. However, the researchers emphasize that their findings should be confirmed in a larger cohort before reaching definitive conclusions. The researchers are continuing to follow healthcare workers after their second dose to better understand how long the vaccine will protect against COVID-19 in different groups of people.

http://bit.ly/3qj8GCC

Ebola is a master of disguise

Faculty of Medicine team from University of Ottawa have discovered a druggable pathway the virus uses to trick its way into our organs

It was once thought that Ebola and related filoviruses were more or less contained to Central Africa. After a West African outbreak and the discovery of Reston ebolavirus in the Philippines, cuevavirus in Spain and various bat filoviruses in China, researchers now understand that this viral family--causing hemorrhagic fevers with up to 90% case fatality rates--has been widespread around the world for millions of years.

Our defenses against it are more embryonic, and though we have a vaccine against one species of Ebola and some therapeutic antibodies on the horizon, both have production or distribution issues. What doctors have been hoping for is a regular drug that can treat Ebola as soon as it rears its terrifying head. A study published today in the journal *PLOS Pathogens*, identifies a pathway that all filoviruses use to gain entry into our cells--and shows how they can be stopped in their tracks by at least one FDA-approved drug.

Ebola is so pernicious because it pulls a fast one on the body, disguising itself as a dying cell.

"It's cloaking itself in a lipid that is normally not exposed at the surface of a cell. It's only exposed when the cell is undergoing apoptosis," says Dr. Marceline Côté, an associate professor in the department of Biochemistry, Microbiology and Immunology, Canada Research Chair in Molecular Virology and Antiviral Therapeutics and the primary investigator on this study. Dr. Côté is a leading global expert on how viruses get into us, an understanding that is key to any effort to keep them out.

The malingering virus is then taken up by immune system cells that unwittingly carry the virus to other parts of the body, disseminating

the infection. Virtually all organs become active sites of replication, and the result is a vicious, multi-system disease. Once it tricks its way into the cell, the virus needs to find a specific receptor that serves as the lock for its glycoprotein key, kicking off the process that will allow it to multiply. A drug that prevents it from any one step in turning that key could defeat the disease.

Dr. Côté's team, in particular PhD student Corina Stewart, tested a library of drugs against a virus in cell cultures. It's not safe to work with a replicating Ebola virus in a regular lab, so the uOttawa team used a surrogate system.

"We use a safe virus disguised as an Ebola virus. They will enter just the same way as an Ebola virus, but actually the inside core when they uncoat is all safe stuff," says Dr. Coté. "It's murine leukemia virus or engineered retroviruses, so nothing to worry about."

Once they found a collection of drugs that seemed to work, they passed the data to collaborator Dr. Darwyn Kobasa at the National Microbiology Laboratory in Winnipeg, where a biosafety level 4 rating allows researchers to handle the bona fide virus. Dr. Kobasa confirmed that a small number of cancer chemotherapy drugs were effective in preventing Ebola from gaining a foothold in the cells.

Though these types of drugs can be tough on the body, an Ebola infection carries a high risk of death. What's more, the infection doesn't last long, so any unpleasant treatment can be similarly brief.

Knowing which drugs worked against Ebola also tells the team more about how the virus gets in. In particular, this study shows that Ebola virus has evolved ways to be active in its invasion of a cell. Previously, it was thought that viral entry was left mostly up to chance, with many particles being left behind while a random few were taken up into the cell. Dr. Côté's study shows the virus has evolved to get in very efficiently, rather than just going along for the ride.

"They are not passive passengers," says Dr. Côté. "They have their hands on the steering wheel."

http://bit.ly/3rV6YYG

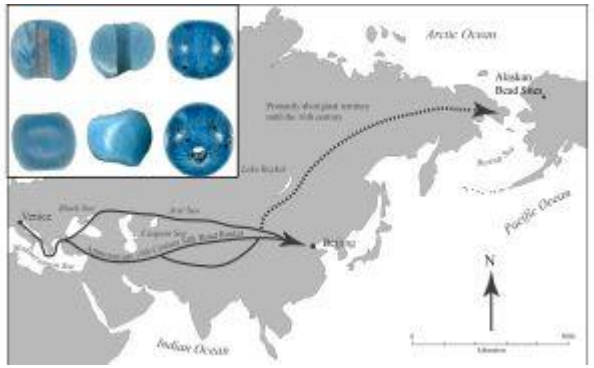
European beads found in Alaska predate Columbus, controversial study claims

These glass beads might be from Venice.

By Laura Geggel - Editor

Brilliantly blue beads from Europe unearthed by archaeologists in Arctic Alaska may predate Christopher Columbus' arrival in the New World, a new controversial study finds.

These blueberry-size beads were likely created in Venice during the 15th century and then traded eastward, enduring a 10,500-mile (17,000 kilometers) land-based journey east across Eurasia and then boated across the Bering Strait to what is now Alaska, according to the study, published online Jan. 20 in the journal American Antiquity.



Archaeologists in Arctic Alaska have found blue beads (top left) from Europe, possibly Venice, that might predate Christopher Columbus' voyage to the New World. **© Beads: Lester Ross and Charles Adkins; Map: Boreal Imagery**

However, other archaeologists dispute the findings, saying while these beads are old, they're not older than Columbus' 1492 voyage.

"These beads cannot be pre-Columbian, because Europeans weren't making beads of this type that early," said Elliot Blair, an assistant professor of anthropology at The University of Alabama, who was not involved in the study.

Instead, these glass beads likely date to the late-16th or early-17th

century, which in itself is a "really cool story," Blair, who specializes in the dating and sourcing of early trade beads in the Americas, told Live Science. "Even with this later dating, an early 17th-century date for these beads is still much earlier than first documented contact between Alaska Natives and Europeans."

Bright blue discovery

Vitus Bering, a Danish explorer serving in the Russian Navy, was thought to be the first modern European to make contact with Alaskan natives when he voyaged there in 1741. But the discovery of the blue beads indicates that people in Asia, possibly those living in the Aboriginal hinterlands or eastern Russia, may have known about Alaska much earlier.

An American archaeologist discovered the first of the blue glass beads in the 1960s, and since then a total of 10 have been unearthed at three Indigenous sites in Alaska's Arctic. Archaeologists have also found other artifacts at these sites, including copper bracelets and bangles, and iron pendants, as well as organic material: twine, animal bones and charcoal, which the researchers dated with radiocarbon.

The discovery of the twine, likely made from shrub willow bark, was key; it's wrapped around part of a blue-beaded bangle, meaning it could provide a date range of when the bangle was made. According to the radiocarbon-dating analysis, the twine likely dates to between 1397 and 1488, said study co-principal investigator Michael Kunz, an archaeologist with the University of Alaska Museum of the North in Fairbanks.

"We were astounded because that was before Columbus had ever even discovered the New World, by several decades," Kunz told Live Science.

After comparing the date ranges from the radiocarbon-dated artifacts — including the twine, two pieces of charcoal and four caribou bones — from the three sites, the researchers found that Indigenous people most likely used these beads between 1443 and 1488, but with potential dates spanning the 14th to 17th centuries.

If the mid-15th-century date is correct, the beads would be the oldest known European products brought to the New World and the oldest record of "drawn" beads, a bead type previously dated to the 16th century, Kunz said.

The team also had five of the beads examined with instrumental neutron activation analysis, a technique that bombards samples with radioactivity and then measures the radioactive decay through the gamma-rays that are emitted, which are unique to each element and can reveal the sample's chemical makeup. The results showed that "the Alaskan beads are made of soda glass, typical of fifteenth-century Venetian and later European manufacture," the researchers wrote in the study.

Perhaps, all of the blue beads came over in one shipment, so to speak, and were traded at a regional Indigenous trading center known as Sheshalik, by the mouth of the Noatak River and Bering Strait; after this initial trading interaction, the beads and their new owners likely dispersed across different parts of Alaska, Kunz said.

"This research that we've done demonstrates that this type of beads — [known as] IIa40 early blue — existed long before they were thought to exist," Kunz said. "That's the bottom line. We're going against the grain. But we have good solid scientific evidence — radiocarbon dating, instrumental neutron activation analysis — that stands behind what we're saying."

Venetian glass?

Other archaeologists say the evidence doesn't add up.

The study "highlights the role of Indigenous exchange networks" of goods from Europe, "but, I also think this paper is a cautionary tale in sensationalizing a story beyond what the evidence supports," Blair said.

Historical and archaeological evidence of drawn beads "strongly

indicates that they weren't manufactured prior to about 1550 at the very earliest," Blair said. "I think it would take very strong evidence to push this date any earlier. The data the authors present doesn't do this, and in fact, the authors' own data is consistent with an early 17th-century date for these beads."

Blair is referring to the twine's radiocarbon dating; although the analysis shows the twine was likely created in the 15th century, it also shows that an early 17th-century date, though less likely, is possible.

In fact, a quick look at the study's radiocarbon date ranges shows that Indigenous Alaskans could have used the beads from 1570 to 1650, a period that fits with production records of European drawn beads, Blair said.

It's not even clear if the beads are from Venice, as the researchers suggest. "It is quite likely that the beads originated in France and not Venice, based on findings at a bead manufacturing site in Rouen," Karlis Karklins, an independent bead researcher and the editor of the Society of Bead Researchers, who was not involved in the study, told Live Science in an email. "Early blue beads (IIa40) containing numerous bubbles were found in bead-making wasters at a site in Rouen, France, which is attributed to the early-17th century. … I do not know of such beads ever having been recovered from archaeological contexts in or around Venice."

There are chemical techniques that could ascertain whether the beads were made in Venice, Blair noted, and those could help solve the mystery of the beads' origin.

The researchers did agree on one thing, however — these beads are the oldest evidence on record of European products in Alaska.

"How they got to distant Alaska from Western Europe in the latter part of the 16th or early-17th century is quite a mystery in itself," Karklins said. "That really invites serious investigation."

http://bbc.in/3akdm5O

Stonehenge: Did the stone circle originally stand in Wales?

One of Britain's biggest and oldest stone circles has been found in Wales - and could be the original building blocks of Stonehenge.

Archaeologists uncovered the remains of the Waun Mawn site in Pembrokeshire's Preseli Hills. They believe the stones could have been dismantled and rebuilt 150 miles (240 km) away on Salisbury Plain, Wiltshire. The discovery was made during filming for BBC Two's Stonehenge: The Lost Circle Revealed.

Prof Pearson said the remains of a cow, which was found at the site, suggested animals may have helped to pull the stones to their resting spot in England

The Welsh circle, believed to be the third biggest in Britain, has a diameter of 360ft (110m), the same as the ditch that encloses Stonehenge, and both are aligned on the midsummer solstice sunrise. Several of the monoliths at the World Heritage Site are of the same rock type as those that still remain at the Welsh site.

And one of the bluestones at Stonehenge has an unusual cross-section which matches one of the holes left at Waun Mawn, suggesting the monolith began its life as part of the stone circle in the Preseli Hills before being moved.

It is already known that the smaller bluestones that were first used to build Stonehenge were transported from 150 miles (240 km) away in modern-day Pembrokeshire.

But the new discovery suggests the bluestones from Waun Mawn could have been moved as the ancient people of the Preseli region migrated, even taking their monuments with them, as a sign of their ancestral identity.

They would then have been re-erected at Stonehenge.

Archaeologists said this could explain why the bluestones, thought to be the first monoliths erected at Stonehenge, were brought from so far away, while most circles are constructed within a short distance of their quarries.

The archaeological investigations as part of the Stones of Stonehenge research project, led by Professor Mike Parker Pearson of University College London, previously excavated two bluestone quarries in the Preseli Hills.

Their discovery that the bluestones had been extracted before the first stage of Stonehenge was built in 3000 BC prompted the team to re-investigate the nearby Waun Mawn stones to see if it was the site of a stone circle supplied by the quarry and later moved.

Only four monoliths remain at the site, but an archaeological dig in 2018 revealed holes where stones would have stood, showing the remaining stones were part of a wider circle of 30-50 stones.

And the scientific dating of charcoal and sediment from the holes reveal it was put up around 3400 BC.

Neolithic people

Findings of the discovery, published in the journal Antiquity, show significant links between Stonehenge and Waun Mawn. It also confirms that the region was an important and densely settled area in Neolithic times until 3000 BC when activity seems to have ceased. Prof Parker Pearson said: "It's as if they just vanished. Maybe most of the people migrated, taking their stones - their ancestral identities - with them."

The Preseli Hills are 150 miles (240 km) from Stonehenge in Wiltshire

Analysis of the remains of people buried at Stonehenge at the time the bluestones were erected there would seem to back up the theory, as it shows some of them were from western Britain, possibly Wales.

With only a few of the Stonehenge stones directly linked to Waun Mawn, the archaeologists also believe monoliths from other stone circles could have been taken from Wales to form part of the new monument.

Prof Parker Pearson said: "With an estimated 80 bluestones put up on Salisbury Plain at Stonehenge and nearby Bluestonehenge, my guess is that Waun Mawn was not the only stone circle that contributed to Stonehenge.

"Maybe there are more in Preseli waiting to be found. Who knows? Someone will be lucky enough to find them."

http://bit.ly/3rWa5iG

Green tea compound aids tumor-suppressing, DNA-repairing protein

Research offers new lead for cancer drug discovery

TROY, N.Y. -- An antioxidant found in green tea may increase levels of p53, a natural anti-cancer protein, known as the "guardian of the genome" for its ability to repair DNA damage or destroy cancerous cells. Published today in *Nature Communications*, a study of the direct interaction between p53 and the green tea compound, epigallocatechin gallate (EGCG), points to a new target for cancer drug discovery.

"Both p53 and EGCG molecules are extremely interesting. Mutations in p53 are found in over 50% of human cancer, while EGCG is the major anti-oxidant in green tea, a popular beverage worldwide," said Chunyu Wang, corresponding author and a professor of biological sciences at Rensselaer Polytechnic Institute. "Now we find that there is a previously unknown, direct interaction between the two, which points to a new path for developing anti-cancer drugs. Our work helps to explain how EGCG is able to boost

p53's anti-cancer activity, opening the door to developing drugs with EGCG-like compounds."

Wang, a member of the Rensselaer Center for Biotechnology and Interdisciplinary Studies, is an expert in using nuclear magnetic resonance spectroscopy to study specific mechanisms in Alzheimer's disease and cancer, including p53, which he described as "arguably the most important protein in human cancer."

P53 has several well-known anti-cancer functions, including halting cell growth to allow for DNA repair, activating DNA repair, and initiating programmed cell death -- called apoptosis -- if DNA damage cannot be repaired. One end of the protein, known as the N-terminal domain, has a flexible shape, and therefore, can potentially serve several functions depending on its interaction with multiple molecules.

EGCG is a natural antioxidant, which means it helps to undo the near constant damage caused by using oxygen metabolism. Found in abundance in green tea, EGCG is also packaged as an herbal supplement.

Wang's team found that the interaction between EGCG and p53 preserves the protein from degradation. Typically, after being produced within the body, p53 is quickly degraded when the N-terminal domain interacts with a protein called MDM2. This regular cycle of production and degradation holds p53 levels at a low constant.

"Both EGCG and MDM2 bind at the same place on p53, the N-terminal domain, so EGCG competes with MDM2," said Wang. "When EGCG binds with p53, the protein is not being degraded through MDM2, so the level of p53 will increase with the direct interaction with EGCG, and that means there is more p53 for anti-cancer function. This is a very important interaction."

"By developing an understanding of the molecular-level mechanisms that control key biochemical interactions linked to devastating illnesses such as cancer and Alzheimer's disease, Chunyu's research is laying the groundwork for new and successful therapies," said Curt Breneman, dean of the Rensselaer School of Science.

"EGCG Binds Intrinsically Disordered N-Terminal Domain of p53 and Disrupts p53-MDM2 Interaction" was published with support from multiple grants from the National Institutes of Health. At Rensselaer, Wang was joined in the research by Lauren Gandy, Weihua Jin, Lufeng Yan, Xinyue Liu, and Yuanyuan Xiao. First author Jing Zhao is a former member of Wang's lab, now on the faculty at China Agricultural University in Beijing, China. Co-first author Alan Blaney is an M.D.-Ph.D. student at Upstate Medical University. Researchers also contributed from SUNY Upstate Medical Center; the University of Massachusetts, Amherst; New York University; the State University of New York at Binghamton; NYU Shanghai; and Merck Research Laboratories.

The authors also wished to credit the extensive collaboration which produced this research, including collaborations with professors Stewart Loh and Michael Cosgrove from Upstate Medical University, Sozanne Solmaz from Binghamton University, Jianhan Chen from University Massachusetts, Amherst, Yingkai Zhang from NYU, and David Ban, a Rensselaer alumni who once worked as an undergraduate researcher in Wang's lab, now a senior scientist at Merck.

http://bit.ly/2OC5DYi

300-Year-Old Pirate Skeletons From Fabled 'Black Sam' Crew Found Off Cape Cod

The remains may include those of the legendary pirate himself, Samuel "Black Sam" Bellamy, a.k.a. "The Robin Hood of the Sea."

By Ed Mazza

The skeletal remains of six pirates who likely served under the legendary Capt. Samuel "Black Sam" Bellamy have been discovered off the coast of Massachusetts.

According to the Whydah Pirate Museum, one set may even be

those of the famed pirate himself, one of the many who perished when his ship, the Whydah Gally, sank off Cape Cod in a storm in 1717. "We hope that modern, cutting-edge technology will help us identify these pirates and reunite them with any descendants who could be out there," explorer Barry Clifford, who found the wreck in 1984, told local media including Boston TV station WHDH.

The remains are encased inside "concretions," or hard masses that form around remains and artifacts, such as this one from the same wreck.

The New England Historical Society said Bellamy thought of himself as the "Robin Hood of the Sea" and called his crew "Robin Hood's men." His other nickname, "Black Sam," came from his signature look: Instead of the powdered wigs in style at the time, he grew out his own black locks.

"Black Sam Bellamy ran his pirate operation democratically," the society noted. "His men were slaves and Indians and sailors pressed into service. Bellamy treated them equally and let them vote on important decisions."

The Whydah itself was a captured slave ship, something noted by Clifford in his announcement of the new discovery. "This shipwreck is very sacred ground," Clifford said, "We know a third of the crew was of African origin and the fact they had robbed the Whydah, which was a slave ship, presents them in a whole new light."

The New England Historical Society said there was no record of Bellamy ever killing a captive even though he took 53 ships and became one of the wealthiest pirates of all time. But that distinction didn't last: He died about a year into his career as a pirate captain.

The wreck was found in 1984 and identified by recovered objects, including the ship's bell.

Scientists thought they had identified some of Bellamy's remains in 2018 when they found a skeleton with a pistol and a pocketful of gold, but DNA tests came back negative. Those remains likely belonged to a member of the pirate crew.

"That bone was identified as a human male with general ties to the Eastern Mediterranean area," author Casey Sherman said in the statement. "These newly found skeletal remains may finally lead us to Bellamy as we now have his DNA."

The wreck site continues to yield new finds, much of which are on display at the Whydah Pirate Museum on Cape Cod.

"At the time of the wreck, she was carrying the picked valuables from over 50 other ships captured by Bellamy's pirates," the museum's website stated. "The Whydah collection, therefore, represents an unprecedented cultural cross-section of material from the 18th century."

A life-size replica of the hull of the pirate ship Whydah Gally is displayed at the Whydah Pirate Museum, in Yarmouth, Mass. **Associated Press**

Last month, The Cape Cod Times described how the finds from the wreck site were examined at the museum, which also displays a replica of the Whydah's hull.

http://bit.ly/3b7zq2n

Researchers propose that humidity from masks may lessen severity of COVID-19

NIH study compares how different face masks affect humidity inside the mask

Masks help protect the people wearing them from getting or spreading SARS-CoV-2, the virus that causes COVID-19, but now researchers from the National Institutes of Health have added evidence for yet another potential benefit for wearers: The humidity created inside the mask may help combat respiratory diseases such as COVID-19.

The study, led by researchers in the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), found that face masks substantially increase the humidity in the air that the mask-wearer breathes in. This higher level of humidity in inhaled air, the researchers suggest, could help explain why wearing masks has been linked to lower disease severity in people infected with SARS-CoV-2, because hydration of the respiratory tract is known to benefit the immune system. The study published in the *Biophysical Journal*.

"We found that face masks strongly increase the humidity in inhaled air and propose that the resulting hydration of the respiratory tract could be responsible for the documented finding that links lower COVID-19 disease severity to wearing a mask," said the study's lead author, Adriaan Bax, Ph.D., NIH Distinguished Investigator. "High levels of humidity have been shown to mitigate severity of the flu, and it may be applicable to severity of COVID-19 through a similar mechanism."

High levels of humidity can limit the spread of a virus to the lungs by promoting mucociliary clearance (MCC), a defense mechanism that removes mucus ? and potentially harmful particles within the mucus ? from the lungs. High levels of humidity can also bolster the immune system by producing special proteins, called interferons, that fight against viruses ? a process known as the interferon response. Low levels of humidity have been shown to impair both MCC and the interferon response, which may be one reason why people are likelier to get respiratory infections in cold weather.

The study tested four common types of masks: an N95 mask, a three-ply disposable surgical mask, a two-ply cotton-polyester mask, and a heavy cotton mask. The researchers measured the level of humidity by having a volunteer breathe into a sealed steel box. When the person wore no mask, the water vapor of the exhaled breath filled the box, leading to a rapid increase in humidity inside the box.

When the person wore a mask, the buildup of humidity inside the box greatly decreased, due to most of the water vapor remaining in the mask, becoming condensed, and being re-inhaled. To ensure no leakage, the masks were tightly fitted against the volunteer's face using high-density foam rubber. Measurements were taken at three different air temperatures, ranging from about 46 to 98 degrees Fahrenheit.

The results showed that all four masks increased the level of humidity of inhaled air, but to varying degrees. At lower temperatures, the humidifying effects of all masks greatly increased. At all temperatures, the thick cotton mask led to the most increased level of humidity.

"The increased level of humidity is something most mask-wearers probably felt without being able to recognize, and without realizing that this humidity might actually be good for them," Bax said.

The researchers did not look at which masks are most effective against inhalation or transmission of the virus and defer to the CDC for guidance on choosing a mask. Earlier studies from Bax and his colleagues showed that any cloth mask can help block the thousands of saliva droplets that people release through simple speech ? droplets that, if released, can remain in the air for many minutes. While the current study did not examine respiratory droplets, it does offer more evidence as to why masks are essential to battling COVID-19.

"Even as more people nationwide begin to get vaccinated, we must remain vigilant about doing our part to prevent the spread of the coronavirus that causes COVID-19," said NIDDK Director Dr. Griffin P. Rodgers. "This research supports the importance of mask-wearing as a simple, yet effective, way to protect the people around us and to protect ourselves from respiratory infection,

especially during these winter months when susceptibility to these viruses increases."

The research was supported by the NIDDK Intramural Research Program and the NIH Intramural Antiviral Target Program.

Courtney, JM and Bax, A. Hydrating the respiratory tract: An alternative explanation why masks lower severity of COVID-19 disease. Biophysical Journal. February 11, 2021.

http://bit.ly/2Zi20ca

Instant death from heart attack more common in people who do not exercise

Active lifestyle is linked with a lower chance of dying immediately from a heart attack

Sophia Antipolis - An active lifestyle is linked with a lower chance of dying immediately from a heart attack, according to a study published today in the *European Journal of Preventive Cardiology*, a journal of the European Society of Cardiology (ESC).1

Heart disease is the leading cause of death globally and prevention is a major public health priority. The beneficial impact of physical activity in stopping heart disease and sudden death on a population level is well documented. This study focused on the effect of an active versus sedentary lifestyle on the immediate course of a heart attack - an area with little information.

The researchers used data from 10 European observational cohorts including healthy participants with a baseline assessment of physical activity who had a heart attack during follow-up - a total of 28,140 individuals. Participants were categorised according to their weekly level of leisure-time physical activity as sedentary, low, moderate, or high.

The association between activity level and the risk of death due to a heart attack (instantly and within 28 days) was analysed in each cohort separately and then the results were pooled. The analyses were adjusted for age, sex, diabetes, blood pressure, family history of heart disease, smoking, body mass index, blood cholesterol, alcohol consumption, and socioeconomic status.

A total of 4,976 (17.7%) participants died within 28 days of their heart attack - of these, 3,101 (62.3%) died instantly. Overall, a higher level of physical activity was associated with a lower risk of instant and 28-day fatal heart attack, seemingly in a dose-response-like manner. Patients who had engaged in moderate and high levels of leisure-time physical activity had a 33% and 45% lower risk of instant death compared to sedentary individuals. At 28 days these numbers were 36% and 28%, respectively. The relationship with low activity did not reach statistical significance.

Study author Dr. Kim Wadt Hansen of Bispebjerg Hospital, Copenhagen, Denmark said: "Almost 18% of patients with a heart attack died within 28 days, substantiating the severity of this condition. We found an immediate survival benefit of prior physical activity in the setting of a heart attack, a benefit which seemed preserved at 28 days."

He noted: "Based on our analyses, even a low amount of leisure-time physical activity may in fact be beneficial against fatal heart attacks, but statistical uncertainty precludes us from drawing any firm conclusions on that point."

The authors said in the paper: "Our pooled analysis provides strong support for the recommendations on weekly physical activity in healthy adults stated in the 2016 European Guidelines on cardiovascular disease prevention in clinical practice;2 especially as we used cut-off values for physical activity comparable to those used in the guidelines."

The guidelines recommend that healthy adults of all ages perform at least 150 minutes a week of moderate intensity or 75 minutes a week of vigorous intensity aerobic physical activity or an equivalent combination thereof.

Dr. Hansen concluded: "There are many ways to be physically active at little or no cost. Our study provides yet more evidence for the rewards of exercise."

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Disclosures: *none declared.*

Notes

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Link will go live on publication: https://academic.oup.com/eurjpc/article-lookup/doi/10.1093/eurjpc/zwaa146

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Alien Cells May Explain COVID 'Brain Fog'

The long-term neurologic symptoms such as "brain fog" experienced by some patients with COVID-19 may be caused by a unique pathology — the occlusion of brain capillaries by large megakaryocyte cells, a new report suggests.

Sue Hughes

The authors report five separate post-mortem cases from patients who died with COVID-19 in which large cells resembling megakaryocytes (*巨核球*) were identified in cortical capillaries. Immunohistochemistry subsequently confirmed their megakaryocyte identity. They point out that the finding is of interest as — to their knowledge — megakaryocytes have not been found in the brain before. The observations are described in a research letter published online February 12 in *JAMA Neurology*.

Bone Marrow Cells in the Brain

Lead author David Nauen, MD, PhD, a neuropathologist from Johns Hopkins University, Baltimore, Maryland, told *Medscape Medical News* he identified these cells in the first analysis of post-mortem brain tissue from a patient who had COVID-19.

"Some other viruses cause changes in the brain such as encephalopathy, and as neurologic symptoms are often reported in COVID-19, I was curious to see if similar effects were seen in brain post-mortem samples from patients who had died with the infection," Nauen said.

On his first analysis of the brain tissue of a patient who had COVID-19, Nauen saw no evidence of viral encephalitis, but he observed some "unusually large" cells in the brain capillaries.

"I was taken aback; I couldn't figure out what they were. Then I realized these cells were megakaryocytes from the bone marrow. I have never seen these cells in the brain before. I asked several colleagues and none of them had either. After extensive literature searches, I could find no evidence of megakaryocytes being in the brain," Nauen noted.

Megakaryocytes, he explained, are "very large cells, and the brain capillaries are very small — just large enough to let red blood cells and lymphocytes pass through. To see these very large cells in such vessels is extremely unusual. It looks like they are causing occlusions."

By occluding flow through individual capillaries, these large cells could cause ischemic alteration in a distinct pattern, potentially resulting in an atypical form of neurologic impairment, the authors suggest.

"This might alter the hemodynamics and put pressure on other vessels, possibly contributing to the increased risk of stroke that has been reported in COVID-19," Nauen said. Although, he reported, none of the samples he examined came from patients with COVID-19 who had had a stroke.

Other than the presence of megakaryocytes in the capillaries, the brain looked normal, he said. He has now examined samples from 15 brains of patients who had COVID-19 and megakaryocytes have been found in the brain capillaries in five cases.

New Neurologic Complication

Classic encephalitis found with other viruses has not been reported

in brain post-mortem examinations from patients who had COVID-19, Nauen noted.

"The cognitive issues such as grogginess associated with COVID-19 would indicate problems with the cortex but that hasn't been documented. This occlusion of a multitude of tiny vessels by megalokaryocytes may offer some explanation of the cognitive issues. This is a new kind of vascular insult seen on pathology, and suggests a new kind of neurologic complication," he added.

The big question is what these megakaryocytes are doing in the brain.

"Megakaryocytes are bone marrow cells. They are not immune cells. Their job is to produce platelets to help the blood clot. They are not normally found outside the bone marrow, but they have been reported in other organs in COVID-19 patients."

"But the big puzzle associated with finding them in the brain is how they get through the very fine network of blood vessels in the lungs. The geometry just doesn't work. We don't know which part of the COVID inflammatory response makes this happen," said Nauen.

The authors suggest one possibility is that altered endothelial or other signaling is recruiting megakaryocytes into the circulation and somehow permitting them to pass through the lungs.

"We need to try and understand if there is anything distinctive about these megakaryocytes — which proteins are they expressing that may explain why they are behaving in such an unusual way," said Nauen.

Noting that many patients with severe COVID-19 have problems with clotting, and megakaryocytes are part of the clotting system, he speculated that some sort of aberrant message is being sent to these cells.

"It is notable that we found megakaryocytes in cortical capillaries in 33% of cases examined. Because the standard brain autopsy sections taken sampled at random [are] only a minute portion of the cortical volume, finding these cells suggests the total burden could be considerable," the authors write.

Nauen added that to his knowledge, this is the first report of such observations, and the next step is to look for similar findings in larger sample sizes.

JAMA Neurol. Published online February 12, 2021. Research Letter

http://wapo.st/37ftYK1

Egypt: Archaeologists unearth ancient beer factory in Abydos

Archaeologists have unearthed what could be the oldest known beer factory at one of the most prominent archaeological sites of ancient Egypt

By Samy Magdy | AP

Cairo — American and Egyptian archaeologists have unearthed what could be the oldest known beer factory at one of the most prominent archaeological sites of ancient Egypt, a top antiquities official said Saturday.

Mostafa Waziri, secretary general of the Supreme Council of Antiquities, said the factory was found in Abydos, an ancient burial ground located in the desert west of the Nile River, over 450 kilometers (280 miles) south of Cairo.

He said the factory apparently dates back to the region of King Narmer, who is widely known for his unification of ancient Egypt at the beginning of the First Dynastic Period (3150 B.C.- 2613 B.C.).

Archaeologists found eight huge units — each is 20 meters (about 65 feet) long and 2.5 meters (about 8 feet) wide. Each unit includes some 40 pottery basins in two rows, which had been used to heat up a mixture of grains and water to produce beer, Waziri said.

The joint mission is co-chaired by Dr. Matthew Adams of the Institute of Fine Arts, New York University, and Deborah Vischak, assistant professor of ancient Egyptian art history and archaeology

at Princeton University.

Adams said the factory was apparently built in this area to provide royal rituals with beer, given that archaeologists found evidences showing the use of beer in sacrificial rites of ancient Egyptians.

British archaeologists were the first to mention the existence of that factory early 1900s, but they couldn't determine its location, the antiquities ministry said.

With its vast cemeteries and temples from the earliest times of ancient Egypt, Abydos was known for monuments honoring Osiris, ancient Egypt's god of underworld and the deity responsible for judging souls in the afterlife.

The necropolis had been used in every period of early Egyptian history, from the prehistoric age to Roman times.

Egypt has announced dozens of ancient discoveries in the past couple of years, in the hope of attracting more tourists.

The tourism industry has been reeling from the political turmoil following the 2011 popular uprising that toppled longtime autocrat Hosni Mubarak. The sector was also dealt a further blow last year by the coronavirus pandemic.